BILAYER TABLET FORMULATION OF METFORMIN HYDROCHLORIDE AND GLIPIZIDE: A NOVEL APPROACH IN THE TREATMENT OF DIABETES

Dissertation work submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY (Pharmaceutics)

MARCH 2010

COLLEGE OF PHARMACY

SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES

Coimbatore – 641044

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Submitted by

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Under the guidance of

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March 2010

COLLEGE OF PHARMACY
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Certificate

This is to certify that the dissertation entitled **"BILAYER TABLET FORMULATION OF METFORMIN HYDROCHLORIDE AND GLIPIZIDE: A NOVEL APPROACH IN THE TREATMENT OF DIABETES"** was carried out by **PHANI KRISHNA YARLAGADDA**, in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and complete satisfaction.

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Above all, I humbly submit my dissertation work, into the hands of ***Almighty****, who is the source of all wisdom and knowledge for the successful completion of my thesis.*

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Y. Phani Krishna

ABBREVIATIONS

API	-	Active pharmaceutical ingredient
CR	-	Controlled release
CRDDS	-	Controlled release drug delivery systems
FTIR	-	Fourier transform infrared spectrometer
HPMC	-	Hydroxy propyl methyl cellulose
Hrs	-	Hours
ICH	-	International Conference on Harmonization
IP	-	Indian pharmacopoeia
IR	-	Immediate Release
JP	-	Japanese pharmacopoeia
MCC	-	Microcrystalline cellulose
MEC	-	Minimum effective concentration
Min	-	Minutes
Ph Eur	-	European pharmacopoeia
q.s	-	Quantum sufficit
SR	-	Sustained Release
SSG	-	Sodium Starch Glycolate
USP	-	United States pharmacopoeia
UV	-	Ultra Violet

LIST OF TABLES

1. INTRODUCTION

In 1985, there were approximately 30 million people with diabetes worldwide; by 1995, this number had escalated to 135 million and by 2025, it is projected that there will be an increase in the incidence of diabetes, affecting 300 million people. Most of the expected increase will be in type 2 diabetes, which accounts for >90% of cases of diabetes, while the incidence of Type 1 diabetes is anticipated to remain stable. By 2025 the countries with largest number of people with diabetes will be in India (>57 million, prevalence 6%), China (>37 million, prevalence 3.4%), and the United States (>21 million, prevalence 8.9%).

Type 2 diabetes, a common disease that combines defects of both insulin secretion and insulin action. It is a progressive illness and most patients will eventually need more than two oral agents to maintain adequate glucose control (Tripathi, 2004). Switching from one drug to another in a patient with poorly control glycemia or maximizing the dosage of an existing drug is only rarely hopeful. Adding medications from different groups to the existing regimen often provides more effective glycemic control. Several of the available oral agents have been studied in the combination and have been shown to further improve glycemic control when compared with monotherapy.

Metformin is the sole member of the biguanide class of medications in the United States. It replaced another biguanide, Phenformin, which was removed from the market because of a propensity for lactic acidosis in 1975 (Bailey CJ, Turner RC, 1996. Stumvoll M, Nurjhan N, 1995).Available in short-acting and sustained-release formulations, it is one of the oldest, and indeed one of the safest, medications used in the treatment of type 2 diabetes.

Metformin exerts its effects primarily by decreasing hepatic glucose output and has a comparatively lesser effect increasing insulin sensitivity. Isotope studies suggest hepatic glucose output is reduced primarily through inhibition of gluconeogenesis, which may be reduced by as much as 75%.-Patients using metformin also exhibit lower fasting insulin concentrations. Most patients using metformin lose weight, and as much as 88% of weight loss with metformin is loss of body fat mass. In patients with normal renal function and who are otherwise healthy, metformin does not increase plasma lactic acid levels or rate of turnover (DeFronzo RA, Goodman AM, 1995). Weight loss occurring during initiation of metformin occurs even without change in energy expenditure.

The major clinical effect of metformin is to decrease fasting glucose levels, thereby reducing hemoglobin A_{1c} (A1C). The degree of clinical effect varies in individual patients, but most patients

experience a reduction in A1C of ~ 1.5 percentage points (Nathan DM, Buse JB, 2006). Because metformin exerts its effects primarily through impairing hepatic gluconeogenesis, it is primarily an antihyperglycemic agent, rather than a hypoglycemic agent, such as insulin or sulfonylureas. As a result, the incidence of hypoglycemia with metformin is quite low. Metformin has additional effects of modest reduction in plasma triglyceride concentrations resulting from decreased production of very-low-density lipoprotein.

The most common reported adverse reaction to metformin therapy is gastrointestinal upset, including nausea, vomiting, anorexia, and diarrhoea. Most patients beginning metformin experience significant mild weight loss, most likely as a result of these effects. The gastrointestinal side effects gradually dissipate in many patients; thus, metformin is generally started in low doses, such as 500-850 mg with breakfast and supper, and are titrated slowly to the maximum dose of 2,550 mg daily. Some patients also describe a metallic taste. Patient compliance, owing in part to a slight decrease in gastrointestinal side effects, may be better with sustained-release metformin than with immediate-release formulations. Sustained-release formulations may be administered once or twice daily (Schwartz S, Fonseca V, 2006).

Lactic acidosis is a rare but potentially fatal complication of metformin therapy. Incidence of this complication is very low: < 1

case per 100,000 treated patients (Salpeter SR, Walsh JM, 2006). Lactic acidosis can be caused by extremely high concentrations of metformin in the bloodstream or by any condition that can induce hypoxia or hepatic insufficiency, thus limiting the body's ability to metabolize lactate.

When lactic acidosis occurs, it is generally in patients who have continued using metformin despite contraindications. Exclusion criteria for metformin therapy include renal insufficiency with creatinine ≥ 1.5 mg/dl in men and 1.4 mg/dl in women, cardiac or pulmonary insufficiency sufficient to cause reduction in peripheral perfusion or central hypoxia, history of lactic acidosis, liver disease, alcohol abuse, or use of intravenous radiographic contrast agents.

Because of metformin's relatively good safety profile, association with weight loss or weight neutrality, and availability as a generic formulation, it is commonly used as an initial agent in type 2 diabetes when lifestyle modification is insufficient to control glucose levels. Recent American Diabetes Association (ADA) consensus guidelines have even suggested starting all eligible newly diagnosed type 2 diabetic patients on metformin in conjunction with efforts to modify lifestyle.

Metformin is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestianl tract, and the absolute bioavailability of a single 500mg dose is reported to be 50% to 60% (Dunn&Piters, 1995). An obstacle to more successful use of metformin therapy is the high incidence of concomitant

gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occur during the initial weeks of treatment. The compound also has relatively short plasma elimination half life of 1.5 to 4.5 hours (Defang, Shufang, &Wei, 2005; Scheen, 1996). Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance.

A sustained release formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once daily dosing of metformin. So SR formulation that releases metformin for 8 to 12 hrs may be suitable for once daily dosing. SR products are needed for metformin to prolong its duration of action and improve patient compliance (Medical Economics Co., 1999; Dunn& Peters, 1995).

Sulfonylureas include several medications that act on β-cells to increase insulin release. They bind to the sulfonylurea receptor on the surface of the β-cell and inhibit potassium efflux, thus depolarizing the β-cells and facilitating insulin release (Aguilar-Bryan L, Nichols C, 1995). First-generation agents, such as acetohexamide, chlorpropamide, and tolbutamide, have largely been replaced by second-generation sulfonylureas, such as glyburide, glipizde, and glimipiride, which have improved safety profiles. Because sulfonylureas act by stimulating insulin release from β-cells, patients without a sufficient number of β-cells, such as those with type 1 diabetes, pancreoprivic diabetes, or later stages of type 2

diabetes, does not respond to these medications. In patients who do respond to them, insulin release may be augmented both in the fasting state and postprandially. Although potencies can vary among sulfonylureas, they tend to lower A1C to a similar extent to metformin, ~ 1.5 percentage points.

Hypoglycemia is the major detrimental effect of these agents. Because different sulfonylureas possess different pharmacotherapeutic profiles, there are differences in risk of hypoglycemic episodes among the different agents. Patients using sulfonylurea medications must be cautioned regarding the signs, symptoms, and risks of hypoglycemia while using these medications. Elderly patients may be at higher risk for hypoglycemia, and patients who frequently skip meals and experience fluctuations in activity level may not be candidates for these medications. Glyburide appears to pose a higher risk of inducing hypoglycemia than other members of this class, possibly because it has a number of active metabolites and high affinity for the sulfonylurea receptor (Gangji AS, Cukierman T, 2007). Hypoglycemia may be recurrent, especially in patients with impaired renal function. Most of these drugs are excreted by the kidney and must be used with considerable caution in patients with renal

insufficiency. Glipizide is often preferred in cases where a sulfonylurea is used in the setting of renal insufficiency.

Another disadvantage of sulfonylureas is the risk of weight gain. Many patients experience an increase ≥ 2 kg after initiation of these medications. There has also been some question as to the possibility that older sulfonylurea medications may increase risks of coronary artery disease. The University Group Diabetes Program study did find an increased association with tolbutamide use and risks of coronary artery events; however, this finding was not supported in the U.K. Prospective Diabetes Study (Diabetes 24 *(Suppl 1)* 1975). It is also noteworthy that some patients with an allergy to sulfonamide medications exhibit cross-reactivity with sulfonylureas; therefore, these drugs are contraindicated in patients with sulfa allergies. There may also be cross-reactivity with other drugs, such as carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics.

An advantage of sulfonylureas, however, is cost. They are all available in generic formulations at relatively low cost to patients, which make them more appealing when cost is a major issue in medication selection. A recent consensus statement from the ADA and the European Association for the Study of Diabetes considered sulfonylurea medications to be second-line agents.

Glipizide is an oral antidiabetic drug of the sulfonylurea class that is used together with diet and exercise to reduce blood glucose

in patients with type 2 diabetes. It stimulates the release of insulin from the pancreas, directing the body to store blood sugar (Siconolfi-Baez, 1990).

A Glipizide and metformin combination is used to treat high blood sugar levels that are caused by type 2 diabetes. Normally, the pancreas releases insulin after eating to help the body store excess sugar for later use. This process occurs during normal digestion of food. In type 2 diabetes, the body does not work properly to store the excess sugar and the sugar remains in the blood stream. Chronic high blood sugar can lead to serious health problems in the future. With two different modes of action, the combination of glipizide and metformin help the body cope with high blood sugar more efficiently.

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable, toxic and have narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels. The goal in designing sustained or controlled delivery is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug

delivery, so, controlled release dosage form is that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Tablets can be designed for use as immediate release products by suitable modification of the composition and manufacturing process and can also be designed as modified release products, with many different potential release patterns.

However, for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with the fluid in the stomach to allow the release of the active drug which then become available, in whole or in part, for absorption from the gastrointestinal tract(GIT). Although most drugs are absorbed from the GIT after passing through the stomach, it is nevertheless important with immediate release products that the tablet disintegrates properly in the stomach to release the drug and allow it to be absorbed quickly after passing through the pyloric sphincter and on into duodenum and beyond.

LITERATURE REVIEW

Aruna A, Nancy K (2000) developed a UV spectrophotometric method based on the measurement of absorbance at 276 nm in pH6.8 phosphate buffer for glipizide, the method obeyed Beer's law in the concentration range 2-30µg/ml.

G Mubeen, Khalika Noor (2009) developed and validated for the estimation of metformin hydrochloride in bulk and in tablet formulation based on the measurement of absorbance at 233nm in pH6.8 phosphate buffer, the method obeyed Beer's law in the range of 2-18µg/ml.

Lewin A, Lipetz R, Schwartz S (2007) compared the extended-release metformin in combination with a sulfonylurea (glyburide) to sulfonylurea monotherapy in adult patients with type 2 diabetes. The purpose of this study was to compare the efficacy and tolerability of extended-release metformin administered with a sulfonylurea monotherpy in patients with type 2 diabetes. They concluded that the combination of biguanide with sulfonylurea was significantly more effective in lowering HbA and glucose levels than sulfonylurea monotherapy in the adult patients with type 2 diabetes. However, a significant increase in the prevalence of hypoglycaemia was observed in the biguanide-sulfonylurea combination treatment groups compared with the sulfonylurea monotherapy group.

Taipei, Taiwan (2006) compared the Sustained-release glipizide therapy to immediate-release glipizide therapy for

treatment of type 2 diabetes mellitus in Chinese patients. The main aim of the study was to compare the efficacy and tolerability of a sustained-release glipizide (GSR) formulation with those of immediate-release glipizide (GIR) in Chinese patients with type2 diabetes mellitus. They concluded that treatment with oral GSR (10mg QD) was not significantly different from that of treatment with GIR (5mg BID) With respect to short term (12 weeks) FPG and HbA(1c) Reductions in Chinese adults with type 2 diabetes mellitus receiving treatment with a sulfonylurea.

M C Gohel, R K Parikh (2007) developed modified release tablets of isoniazid using hydroxypropyl methyl cellulose as a release controlling agent. The low-viscosity grade Hydroxypropyl methyl cellulose, medium viscosity HPMC, and high-viscosity grade HPMC were used to prepare the matrix tablets. The tablets prepared by direct compression, were subjected to physical characterization and *in-vitro* drug release studies. The in-vitro drug release was carried out in pH6.8 alkaline dissolution medium. The polymer type did not affect the flow of powder blend and the concentration of the polymer. The viscosity grade of HPMC and the drug release was inversely correlated.

Abul Kalam Lutful Kabir, Tasbira Jesmeen (2008) formulated the oral sustained-release Metformin hydrochloride matrix tablets by using hydroxypropyl methyl cellulose as rate controlling polymer. The tablets were prepared by direct compression technique. The tablets were subjected to thickness, weight variation test, drug content etc and showed satisfactory results. The results indicated that

a decrease in release kinetics of the drug was observed by increasing the polymer concentration.

D Choudhary, S Kumar, GD Gupta (2009) attempted to improve the solubility and dissolution of glipizide by solid dispersion (kneading) technique. Poloxamer 188 and Poloxamer 407 were used as the carriers. The glipizide-poloxamer solid dispersion was characterized by FT-IR, Scanning Electron Microscopy and *in-vitro* dissolution studies. The results show that Sds prepared in this study were found to have better dissolution rates in comparison to intact glipizide and physical mixture of PXM 188 and PXM 407.

Ganesh Chaulang, Piyush PateL, Sharwaree Hardikar (2009) formulated solid dispersions of Furosemide in Sodium Starch Glycolate using Kneading method. This study shows that the dissolution rate of furosemide can be enhanced considerably by formulating in it as a solid dispersion in SSG using kneading method. Incorporation of Superdisintegrants in the solid dispersions played a critical role in dissolution enhancement. It may be feasible to prepare suitable formulations of furosemide solid dispersions as fast dissolving tablets.

Marina Levina, Fiona Palmer, (2005) formulated sustained release metformin hydrochloride tablets by direct compression technique using HPMC as rate controlling polymer. The matrix formulations were compared to a commercially available ER metformin hydrochloride tablets Glucophage and concluded that

matrix tablets prepared using Methocel K100M produced consistent and robust extended release.

PURPOSE AND PLAN OF WORK

AIMS AND OBJECTIVES

- The present work relates to the development of a formulation for the effective treatment of Type2 Diabetes.
- The formulation involves the development of Metformin hydrochloride (SR) and Gipizide (IR) as bilayer tablet.
- Metformin hydrochloride has poor compressibility and present formulation problems.

  Present study aims at development of direct compression metformin hydrochloride using different excipients and enhancing the flow and compaction process, which helps in development of bilayer tablet.
- Glipizide have very low solubility and as a result low dissolution rate. Solubility of Glipizide should be increased in order to improve the dissolution rate.
- An effort to increase the solubility and dissolution rate of glipizide in order to increase the oral bioavailability is needed.

  The present work aims to evaluate the potential of the solid dispersion technique for development of immediate release using Sodium Starch Glycolate as hydrophilic carrier for developing a bilayer tablet.

PLAN OF WORK

1. Preparation of standard graph for the drug Metformin hydrochloride using UV spectrophotometry.
2. Preparation of Metformin hydrochloride SR tablets by direct compression method.
3. Evaluation of the physical characteristics.
4. Compatibility study using Infra Red (IR) spectroscopy.
5. Tablet assessed with respect to physical parameters such as Friability studies, FT-IR Studies, Tablet thickness, Weight variation test, Drug content assay, Hardness, Friability, *In-Vitro* release, dissolution kinetics.
6. Optimization of the Metformin hydrochloride sustained release tablets
7. Preparation of standard graph for the drug Glipizide using UV spectrophotometry.
8. Preparation of Glipizide immediate release tablets by Solid dispersion (kneading) method.
9. Evaluation of the physical characteristics.
10. Compatibility study using Infra Red (IR) spectroscopy.
11. Tablet assessed with respect to physical parameters such as Friability studies, FT-IR Studies, Tablet thickness, Weight variation test, Drug content assay, Hardness, Friability, *In-Vitro* release, dissolution kinetics.

12. Optimization of the Glipizide immediate release tablets.
13. Preparation of final bilayer tablets using optimized formulations of Metformin hydrochloride and Glipizide and their evaluation.

METFORMIN (USP 2000)

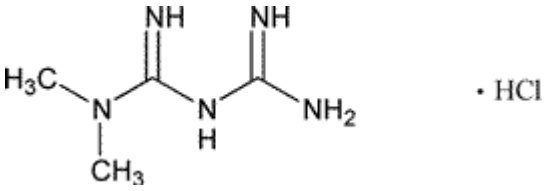
Chemical Formula:

$C_4H_{11}N_5$

Chemical Name

1-(diaminomethylidene)-3, 3-dimethyl-guanidine

Chemical Structure



Molecular Weight

129.164 g/mol

Physical State

Solid

Melting Point

223-226^{0}C

Water Solubility

Freely soluble as HCl salt

Isoelectric Point

12.4

Drug Category

- Hypoglycemic Agents

Dosage Forms

- Extended release tablet (500 mg or 1000 mg)

Pharmacology

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

Mechanism of Action

Metformin's pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Absorption

Absorbed over 6 hours, bioavailability is 50 to 60% under fasting conditions. Food delays absorption.

Toxicity

Acute oral toxicity (LD_{50}): 350 mg/kg [Rabbit]. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen.

Drug Interactions

(Clinical Evaluation of Drug Interactions Conducted with metformin)

Furosemide - A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide

renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine - A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs - Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics.

GLIPIZIDE (USP 2000)

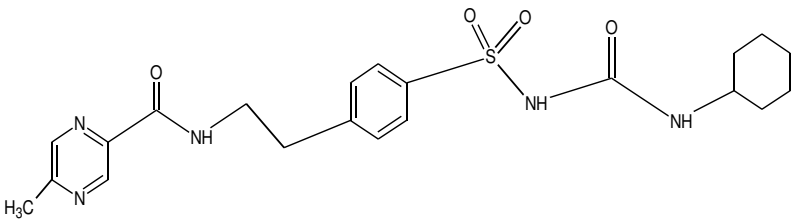
Chemical Formula

$C_{21}H_{27}N_5O_4S$

Chemical Name

N-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-5-methyl-pyridine-2- carboxamide

Chemical Structure



Molecular Weight

444.548 g/mol

Physical State

Solid

Melting Point

208-209^{0}C

Water Solubility

37.2 mg/L

Isoelectric Point

5.9

Drug Category

- Hypoglycemic Agents

Dosage Forms

- Immediate-release oral tablets
- Extended-release oral tablets

Pharmacology

Glipizide, a second-generation sulfonylurea, is used with diet to lower blood glucose in patients with diabetes mellitus type II. The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. Some patients fail to

respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide.

Mechanism of Action

Sulfonylureas likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin.

Absorption

Gastrointestinal absorption is uniform, rapid, and essentially complete.

Toxicity

The acute oral toxicity was extremely low in all species tested (LD50 greater than 4 g/kg). Overdosage of sulfonylureas including glipizide can produce hypoglycemia.

Drug Interactions

Immediate and Extended Release Tablets

The hypoglycaemic action of sulfonylurea's may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles and other drugs that are highly

bound salicylates, sulphonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving glipizide, the patient should be observed closely for hypoglycaemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

HYPROMELLOSE

Nonproprietary Names

BP : Hypromellose

JP : Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP : Hypromellose

Synonyms

Benecel MHPC; hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; merthyl hydroxypropylcellulose; Metolose ; Pharmacoat ; Spectracel 6 ; Spectracel 15; Tylopur.

Chemical Name and CAS registry number

Cellulose, 2-hydroxypropyl-methyl ether [9004-65-3]

Functional category

Coating agent; film-former; rate – controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

Viscosity (dynamic):

Wide ranges of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used

to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions;

Methocel grade	Nominal	Viscosity (MPa s)
K 100LVP	100	80-120
K4M	4000	3000-5600
K15MP	15000	12000-2100
K100MP	100 000	80 000-120 000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90C, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When water miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to part of hypromellose. Cold water is then added to produce the required volume.

CELLULOSE, MICROCRYSTALLINE

Nonproprietary Names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibroce*l*; Pharmacel; Tabulose; Vivapur.

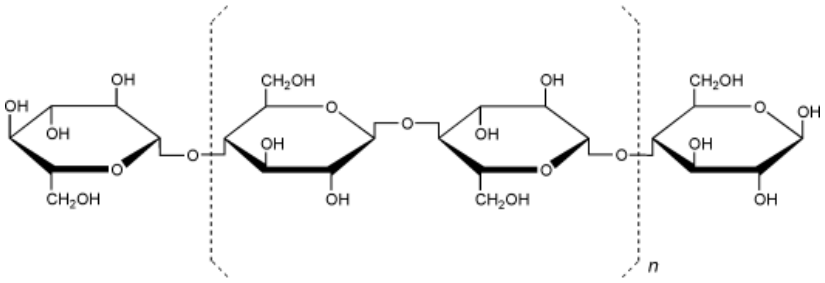
Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000. Where $n \approx 220$.

Structural Formula



Functional Category

Adsorbent; Suspending agent; Tablet and Capsule Diluent; Tablet Disintegrant.

Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Uses of microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

MAGNESIUM STEARATE

Nonproprietary Names

BP : Magnesium stearate

JP : Magnesium stearate

PhEur : Magnesii stearas

USPNF : Magnesium stearate

Synonyms

Magnesium Octadecanoate; Octadecanoic Acid, Magnesium Salt; Stearic Acid, Magnesium salt.

Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category

Tablet and Capsule Lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Typical Properties

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

TALC

Nonproprietary Names:

BP	:	Purified talc
JP	:	Talc
PhEur	:	Talcum
USPNF	:	Talc

Synonyms

Magsil osmanthus, Magsil star, powdered talc.

Chemical Name and CAS Registry Number

Talc [14807- 96- 6]

Structural Formula

$Mg_6(Si_2O_5)_4(OH)_4$

Functional Category

Glidant, Anticaking agent, Capsule and tablet diluents & Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

It is widely used in oral solid dosage formulation as glidant and diluents. It is also used in topical preparation of dusting powder, although it should not be dust in surgical gloves. It is additionally used to clarify liquid and is also used only for its lubricant properties in cosmetics and food products.

Uses of Talc

Use	Concentration (%)
Talcum powder	90–99
Tablet lubricant	1–10
Tablet & capsule diluents	5-30

Sodium Starch Glycolate

Nonproprietary Names

BP : Sodium starch glycollate

PhEur : Carboxymethylamylum natricum

USPNF : Sodium starch glycolate

Synonyms

Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 mm in diameter, with some less-spherical granules ranging from 10–35 mm in diameter.

MATERIALS AND EQUIPMENTS

MATERIALS

Material	Source
Metformin	Granules India Limited, Hyderabad.
Glipizide	Franco-Indian Pharmaceuticals, Chennai.
HPMC K100m	Himedia Laboratories, Mumbai.
HPMC K15m	Himedia Laboratories, Mumbai.
HPMC K4m	Himedia Laboratories, Mumbai.
Microcrystalline cellulose	SD Fine Chemicals, Mumbai.
Sodium Starch Glycolate	SD Fine Chemicals, Mumbai.
Magnesium Stearate	SD Fine Chemicals, Mumbai.
Talc	SD Fine Chemicals, Mumbai.
Silica Gel	SD Fine Chemicals, Mumbai.

Equipments

Equipment	Model/company
Tablet punching machine	Rimek mini press
UV-Visible spectrophotometer	Jasco V-530
FT-IR spectrophotometer	Jasco-FT-IR 8201 PC
Digital balance	Denver instruments
Dissolution test apparatus	Lab India Disso 2000
Pfizer hardness tester	Scientific Engineering Corporation
Friability tester	Remi equipments

I. ESTIMATION OF METFORMIN HYDROCHLORIDE USING UV SPECTROPHOTOMETRY (G Mubeen, 2009)

a. Preparation of Stock Solution

Accurately weigh 100mg of Metformin hydrochloride and transfer to a 100ml volumetric flask and then add phosphate buffer pH 6.8 to dissolve the drug and then make up the volume up to 100ml with phosphate buffer pH6.8, this gives the stock solution l (1000µg/ml).

b. Preparation of Standard Solution

From stock solution l, pipette out 1ml and transfer to 100ml standard volumetric flask. Make up the volume to 100ml with phosphate buffer pH6.8; this gives the stock solution ll (10µg/ml). From the stock solution ll, pipette out 0.2, 0.4, 0.6, 0.8 and 10 ml into 5 separate 10 ml volumetric flasks respectively, then make up the volume up to the mark with phosphate buffer pH 6.8 to give 2, 4, 6, 8, and 10 µg/ml concentration solutions and the phosphate buffer pH6.8 was taken as blank.

The absorbance was measured at 233nm and the graph was plotted with concentration (µg/ml) vs absorbance.

II. ESTIMATION OF GLIPIZIDE USING UV SPECTROPHOTOMETRY (Aruna A, 2000)

a. Preparation of Stock Solution

Accurately weigh 100mg of Glipizide and transfer to a 100ml volumetric flask and then add phosphate buffer pH 6.8 and minimum quantity of methanol to dissolve the drug and then make up the volume up to 100ml with phosphate buffer pH6.8, this gives the stock solution l (1000µg/ml).

b. Preparation of Standard Solution

From stock solution l, pipette out 1ml and transfer to 100ml standard volumetric flask. Make up the volume to 100ml with phosphate buffer pH6.8; this gives the stock solution ll (10µg/ml).

From the stock solution ll, pipette out 0.2, 0.4, 0.6, 0.8 and 10 ml into 5 separate 10 ml volumetric flasks respectively, then make up the volume up to the mark with phosphate buffer pH 6.8 to give 2, 4, 6, 8, and 10 µg/ml concentration solutions and the phosphate buffer pH6.8 was taken as blank. The absorbance was measured at 276nm and the graph was plotted with concentration (µg/ml) vs absorbance.

III. COMPATIBILITY STUDIES

Before formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically characterized. Compatibility studies give the information needed to define the nature of the drug substances and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility.

Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction between Metformin and Glipizide and with their excipients respectively.

Weighed amount of drug (3 mg) was mixed with 100 mg of potassium bromide (dried at 40-50C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm^{-1} in IR spectrophotometer (Silverstein).

IV. COMPOSITION OF VARIOUS TRIAL FORMULATIONS FOR THE SR LAYER CONTAINING METFORMIN HYDROCHLORIDE

Metformin hydrochloride tablets are prepared by using direct compression technique. Different grades of HPMC like K4M, K15M, and K100M are used as the rate controlling polymer or as matrix formers. Other polymers like microcrystalline cellulose is used as water-insoluble filler, lubricants and glidants like Silica gel and magnesium stearate are used as the other excipients. All the ingredients are uniformly mixed and subjected for direct compression.

V. EVALUATION OF METFORMIN HYDROCHLORIDE SR TABLETS

The formulated tablets were subjected for the following quality control tests:

a. Weight variation
b. Hardness

c. Friability
d. Drug content uniformity
e. Disintegration
f. *In vitro* dissolution studies

a. Weight variation test

The USP weight variation test is run by weighing tablets 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The weight variation of tablets more than 324 mg allowed as per USP limit is ±5%.

b. Hardness test

Pfizer hardness tester was used for measuring the hardness of formulated tablets. Five tablets were taken randomly and subjected to test.

c. Friability

The pre weighed tablets are placed in the tumbling chamber which is rotated for four minutes or for 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets are again weighed and the loss in weight indicates the friability. The acceptance limit of weight loss should not be more than 0.5 to 1%.

d. Drug content Uniformity

Weigh and powder 20 tablets. Weigh accurately aquantity of powder containing about.1 gm of metformin, shake with 70ml of water for 15 min, dilute to 100 ml with water and filter. Dilute 10ml

of the filtrate to 100ml with water. Further dilute 10 ml to 100ml with water and measure the absorbance of the resulting solution at the maximum about 232nm. Calculate the content of Metformin hydrochloride taking 798 as a specific absorbance at 232nm.

e. Disintegration Test

Six tablets are taken in disintegration apparatus. Six glass tubes that are 3 inches long open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test the disintegration time one tablet is placed in each tube, and the basket rack is positioned in a 1litre beaker of water at 37^0C ± 2^0C such that the tablets remain2.5 cm from the bottom of the beaker. A standard motor driver device is used to move the basket assembly up and down through a distance of 5-6cm at a frequency of 28-32 cycles per minute. To meet the USP standard all particles of tablet must pass through 10 mesh screen in the time specified. For uncoated tablets the USP time standard is 5minutes. But majority of tablets have maximum disintegration time for 30 minutes.

f. *In vitro* Dissolution Study

The release of Metformin hydrochloride from the SR tablets was studied in 900 ml of dissolution medium using a USP dissolution paddle assembly (Lab India Disso 2000) instrument at 50 rpm and 37±0.5°C. The dissolution medium used was phosphate buffer pH6.8.

Samples of dissolution medium were withdrawn at suitable time interval and was then determined spectrophotometrically at 233 nm. Graph was plotted with time vs percentage drug released.

VI. COMPOSITION OF VARIOUS TRIAL FORMULATIONS FOR THE IR LAYER CONTAINING GLIPIZIDE

Glipizide tablets are prepared by using kneading method of solid dispersion technique. Glipizide and sodium starch glycolate were triturated using a small volume of methanol-water (1:1) solution to obtain a thick paste, which was kneaded for 30 min and then dried at 40ºC in an oven. The dried mass was then pulverized, passed through mesh no 30.

The prepared solid dispersion is mixed with other ingredients like microcrystalline cellulose; talc and colouring agent tartrazine are added and uniformly fixed. 100mg is accurately weighed from the above mixture and the tablets were punched using Rimek mini press.

VII. EVALUATION OF GLIPIZIDE IR TABLETS

The formulated tablets were subjected for the following quality control tests:

a. Weight variation
b. Hardness
c. Friability
d. Drug content uniformity
e. Disintegration
f. *In vitro* dissolution studies

a. Weight variation test

The USP weight variation test is run by weighing tablets 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The

weight variation of tablets less than 130 mg allowed as per USP limit is ±10%.

b. Hardness test

Pfizer hardness tester was used for measuring the hardness of formulated tablets. Five tablets were taken randomly and subjected to test.

c. Friability

The pre weighed tablets are placed in the tumbling chamber which is rotated for four minutes or for 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets are again weighed and the loss in weight indicates the friability. The acceptance limit of weight loss should not be more than 0.5 to 1%.

d. Drug content Uniformity

The prepared tablets containing glipizide was tested for drug content uniformity. Tablets were dissolved in 100 ml of methanol in 100 ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 276 nm in a Jasco V530 UV visible spectrophotometer.

e. Disintegration Test

Six tablets are taken in disintegration apparatus. Six glass tubes that are 3 inches long open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test the disintegration time one tablet is placed in each tube, and the

basket rack is positioned in a 1litre beaker of water at 37^0C ± 2^0C such that the tablets remain2.5 cm from the bottom of the beaker. A standard motor driver device is used to move the basket assembly up and down through a distance of 5-6cm at a frequency of 28-32 cycles per minute. To meet the USP standard all particles of tablet must pass through 10 mesh screen in the time specified. For uncoated tablets the USP time standard is 5minutes. But majority of tablets have maximum disintegration time for 30 minutes.

f. *In vitro* Dissolution Study

The release of glipizide from the tablets was studied in 900 ml of dissolution medium using a USP dissolution paddle assembly (Lab India Disso 2000) instrument at 50 rpm and 37±0.5°C. The dissolution medium used was phosphate buffer pH6.8.

Samples of dissolution medium were withdrawn at suitable time interval and was then determined spectrophotometrically at 276 nm. Graph was plotted with time vs percentage drug released.

VIII. Formulation of Bilayer Tablet of Metformin Hydrochloride (SR) and Glipizide (IR)

Final bilayer tablets were prepared using optimized formulations of Metformin hydrochloride (F_3) and Glipizide (F_4). Initially Metformin hydrochloride was compressed very slightly followed by addition of Glipizide to it and compressed finally to get a bilayer tablet (F7).

IX.EVALUATION OF BILAYER TABLET CONTAINING METFORMIN HYDROCHLORIDE (SR) AND GLIPIZIDE (IR) TABLETS

The evaluation tests performed for the Metformin hydrochloride SR tablets and Glipizide IR tablets are repeated for the bilayer tablet containing Metformin hydrochloride (SR) and Glipizide (IR).

I. ESTIMATION OF METFORMIN HYDROCHLORIDE USING UV SPECTROPHOTOMETRY

Metformin hydrochloride was estimated using phosphate buffer pH6.8 and measured at 233nm using UV spectrophotometry. It obeyed the Beer's law in the range of 2-10µg/ml. Slope was found to be 0.0784 and the correlation coefficient was found to be 0.9999 and the results were given in table 1.

Table 1: Estimation of Metformin hydrochloride measured at 233nm using UV spectrophotmetry

S. No	Concentration (µg/ml)	Absorbance at 233nm
1	0	0.000
2	2	0.151
3	4	0.312
4	6	0.471
5	8	0.625
6	10	0.781

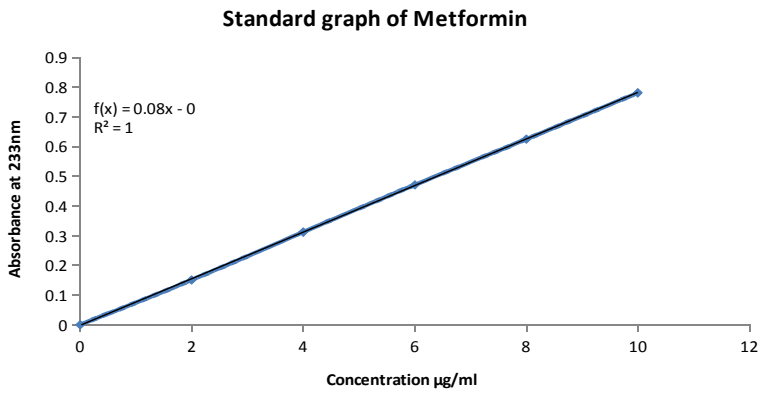


Fig 1: Estimation of Metformin hydrochloride measured at 233nm using UV spectrophotmetry.

II. ESTIMATION OF GLIPIZIDE USING UV SPECTROPHOTOMETRY

Glipizide was estimated using phosphate buffer pH6.8 and measured at 276nm using UV spectrophotometry. It obeyed the Beer's law in the range of 2-10µg/ml. Slope was found to be 0.023 and the correlation coefficient was found to be 0.9997 and the results were given in table 2.

Table 2: Estimation of Glipizide measured at 276nm using UV spectrophotmetry

S. No	Concentration (µg/ml)	Absorbance at 276nm
1	0	0.000
2	2	0.048
3	4	0.091
4	6	0.141
5	8	0.184
6	10	0.231

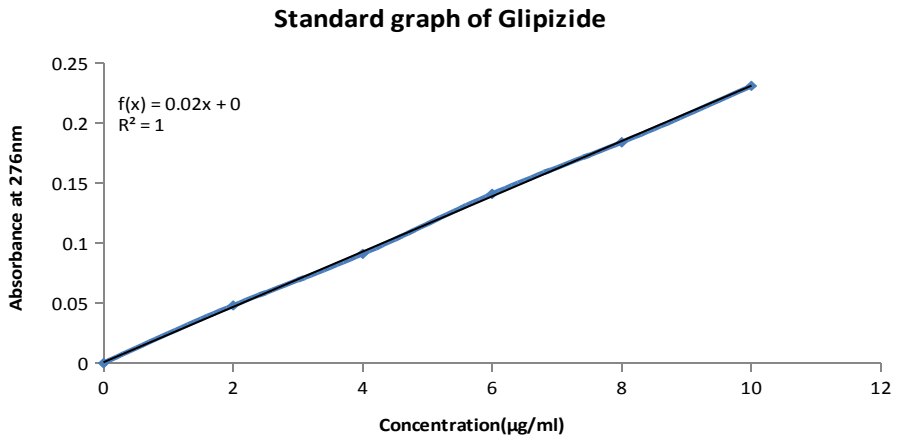


Fig 2: Estimation of Glipizide measured at 276nm using UV spectrophotmetry.

III. COMPATIBILITY STUDIES

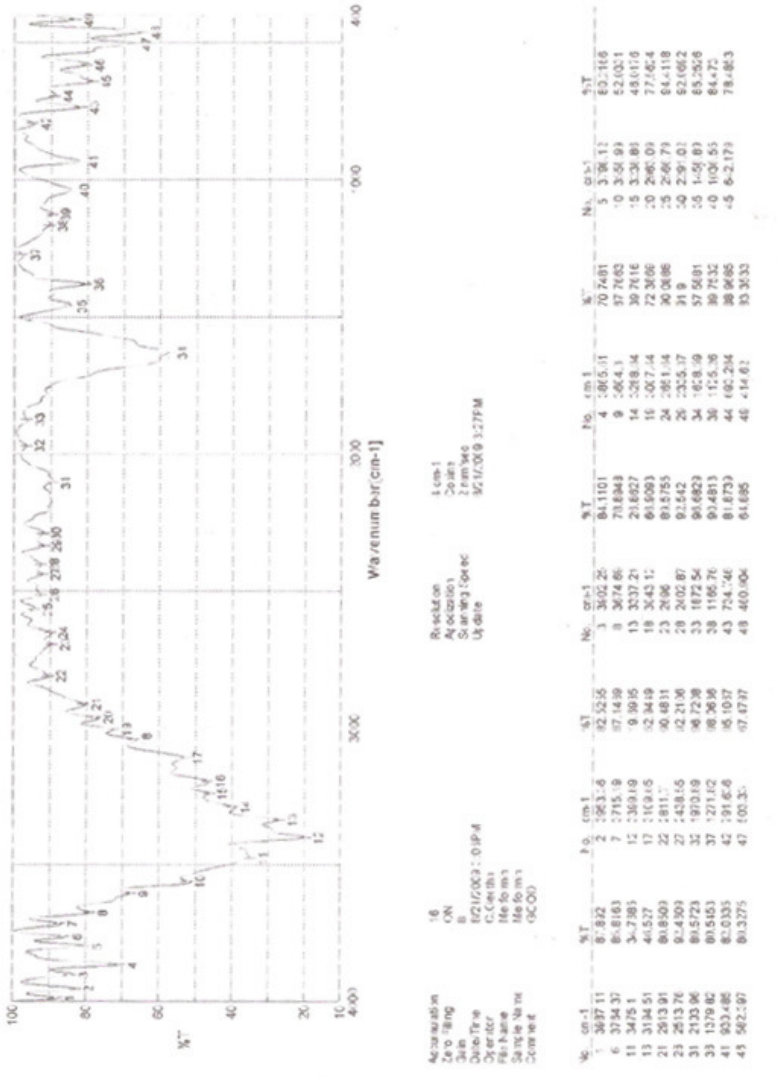


Fig3: Infra red spectrum of Metformin hydrochloride

NH_2 1^0 amine stretch occurs between 3500-3400 cm^{-1} (Silverstein). In the above figure primary amine was found at peak 12 at 3399.89 cm^{-1}.

Aliphatic CH stretch occurs between 2962-2872 cm^{-1}. In the above figure the aliphatic CH stretch was found at peak 20 at 2963 cm^{-1}.

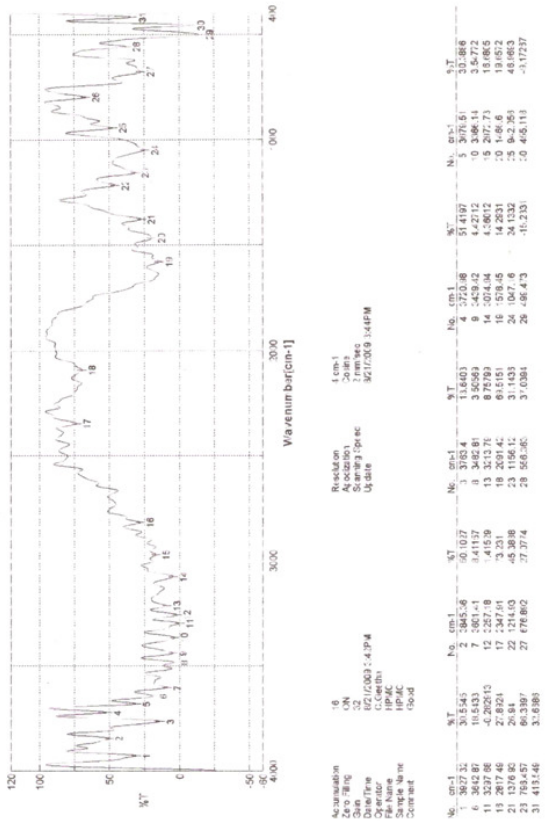


Fig 4: Infra red spectrum of Metformin hydrochloride and HPMC

NH_2 1^0 amine stretch occurs between 3500-3400 cm^{-1}. In the above figure primary amine was found at peak 8 at 3482.81 cm^{-1}.

Aliphatic CH stretch occurs between 2962-2872 cm^{-1}. In the above figure the aliphatic CH stretch was found at peak 15 at 2972 cm^{-1}.

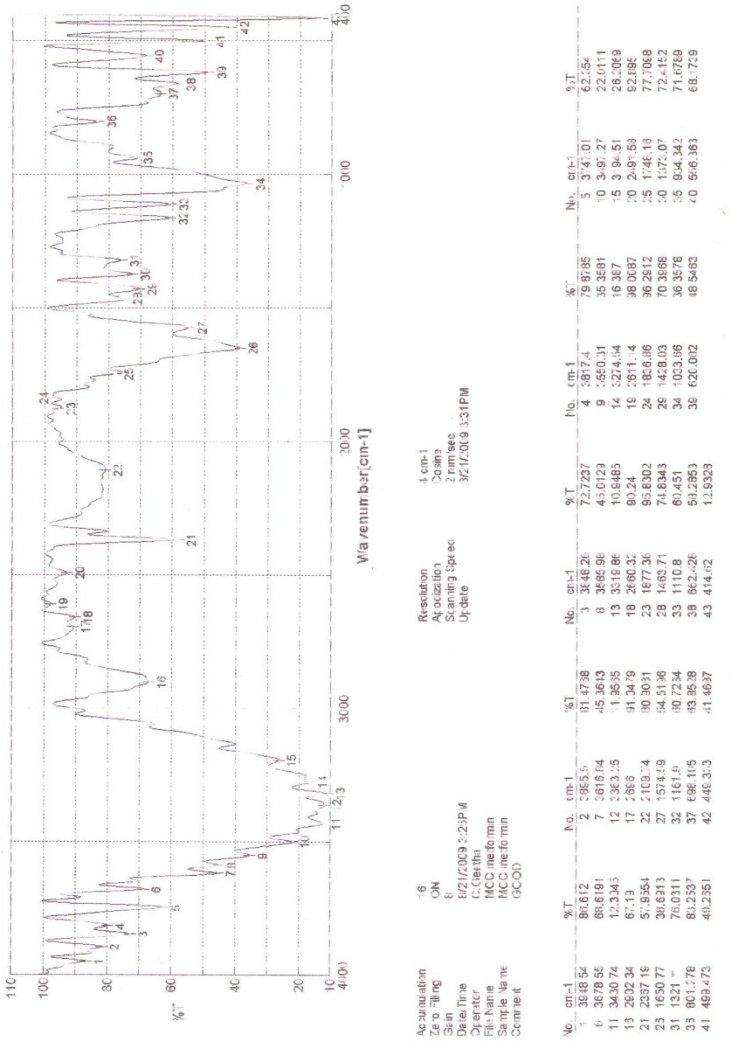


Fig 5: Infra red spectrum of Metformin hydrochloride and Micro crystalline cellulose.

NH_2 1^0 amine stretch occurs between 3500-3400 cm^{-1}. In the above figure primary amine was found at peak 10 at 3497 cm^{-1}.

Aliphatic CH stretch occurs between 2962-2872 cm^{-1}. In the above figure the aliphatic CH stretch was found at peak 16 at 2902 cm^{-1}.

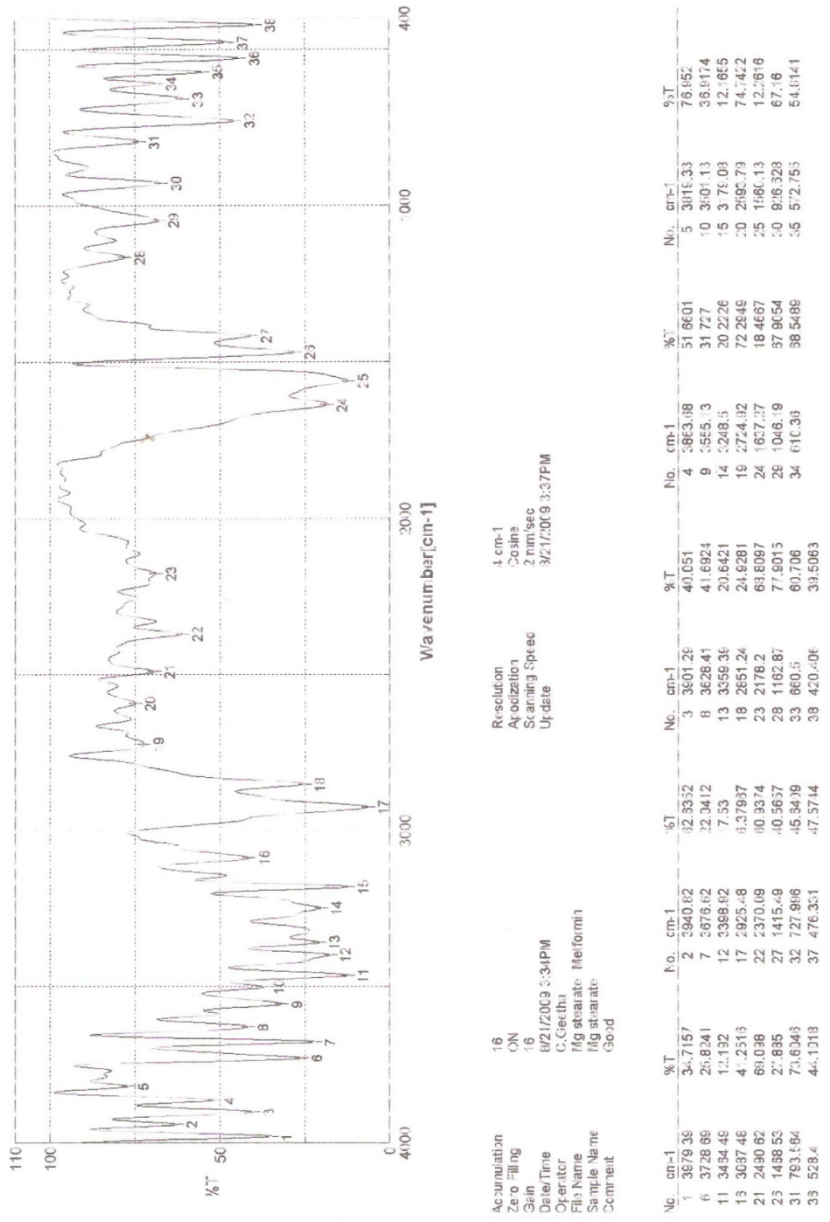
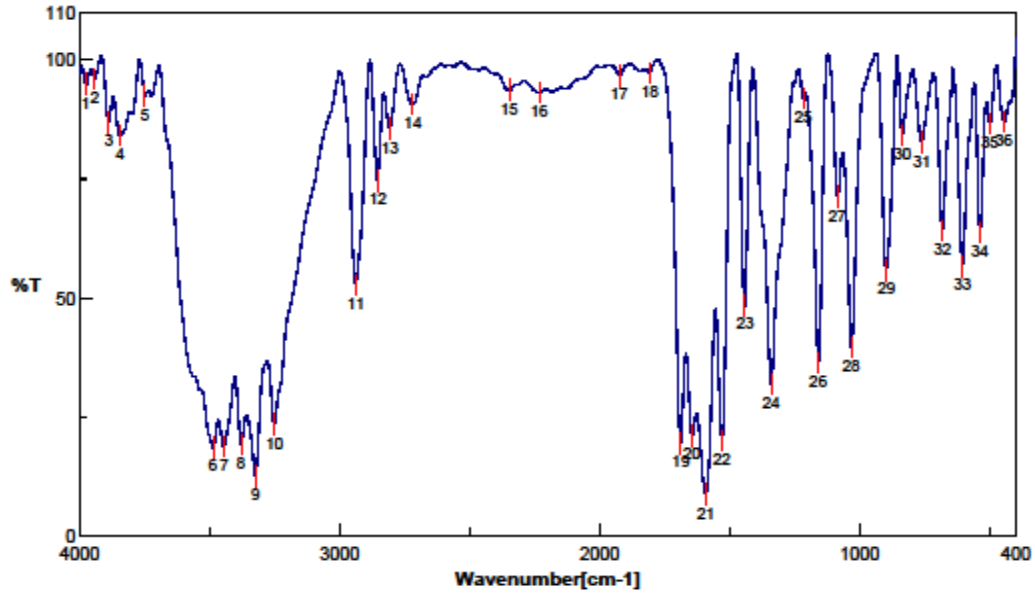


Fig 6: Infra red spectrum of Metformin hydrochloride and Magnesium stearate

NH_2 1^0 amine stretch occurs between 3500-3400 cm^{-1}. In the above figure primary amine was found at peak 11 at 3464 cm^{-1}.

Aliphatic CH stretch occurs between 2962-2872 cm^{-1}. In the above figure the aliphatic CH stretch was found at peak 17 at 2925 cm^{-1}.



Accumulation	16
Resolution	16 cm-1
Zero Filling	ON
Apodization	Cosine
Gain	8
Scanning Speed	2 mm/sec
Date/Time	1/19/2010 11:01AM
Update	1/19/2010 0:06PM
Operator	C.Geetha
File Name	Glipizide
Sample Name	Glipizide
Comment	

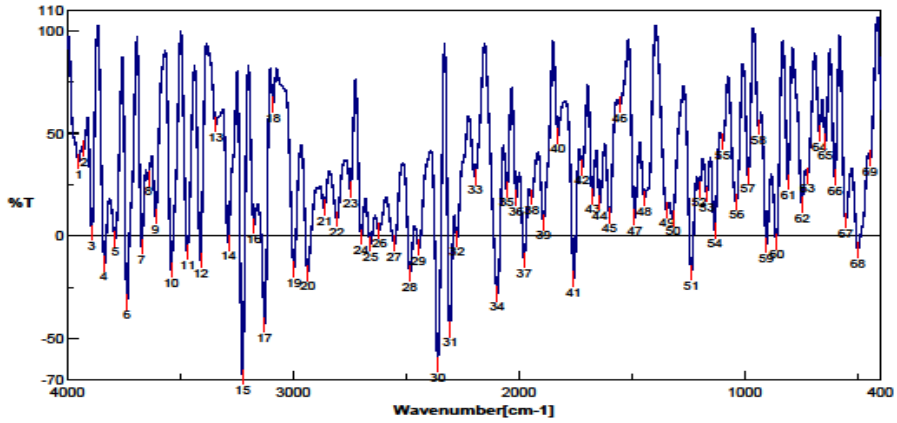
No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3976.5	94.9703	2	3941.79	96.0895	3	3887.79	86.9363
4	3845.36	84.2553	5	3748.94	92.4664	6	3486.67	18.5775
7	3444.24	18.8497	8	3378.67	19.1196	9	3324.68	12.4637
10	3251.4	23.4674	11	2938.98	52.7647	12	2854.13	74.6923
13	2807.85	85.6247	14	2719.14	90.7355	15	2348.87	93.7497
16	2233.16	93.1738	17	1924.61	96.7009	18	1808.9	97.3656
19	1689.34	19.4155	20	1646.91	21.1238	21	1592.91	8.69965
22	1531.2	19.9656	23	1442.49	48.4104	24	1342.21	31.9565
25	1218.79	91.9517	26	1160.94	36.369	27	1087.66	71.2876
28	1033.66	39.6052	29	898.666	55.8604	30	836.955	84.2046
31	763.673	82.6546	32	682.677	64.2172	33	605.539	56.6189
34	539.971	63.815	35	501.401	86.5902	36	447.404	86.9826

Fig 7: Infra red spectrum of Glipizide

S=O stretch of sulphonamides occurs at 1370-1335 cm^{-1}. In the above spectrum S=O stretch can be noticed at peak number 24 at 1342 cm^{-1}.

C=O stretch of amide occurs at 1689.34 cm^{-1}.

Aliphatic CH stretch occurs at 2962 and 2872 cm^{-1}. In the above spectrum the CH stretch can be noticed at peak 11 at 2938 cm^{-1}.



Accumulation	16
Resolution	16 cm-1
Zero Filling	ON
Apodization	Cosine
Gain	256
Scanning Speed	2 mm/sec
Date/Time	1/19/2010 11:47AM
Update	1/19/2010 0:08PM
Operator	C.Geetha
File Name	Glipizide+MCC
Sample Name	Glipizide+MCC
Comment	

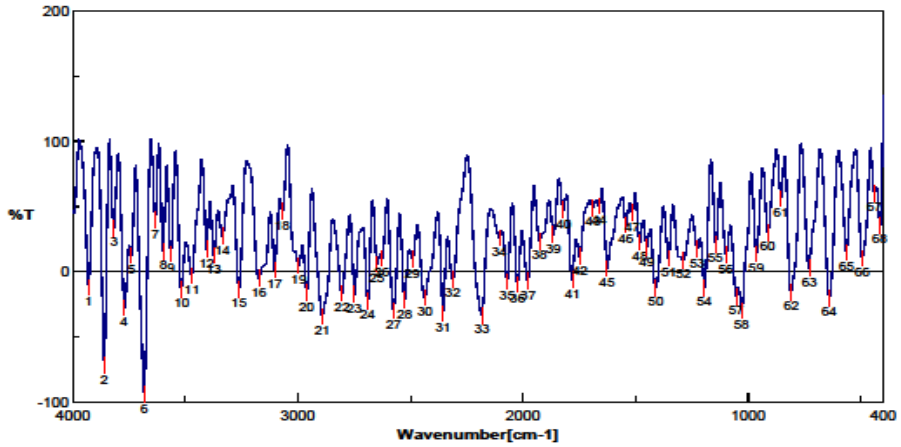
No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3949.5	36.47	2	3926.36	42.6242	3	3891.65	1.50877
4	3837.65	-13.3658	5	3787.51	-1.28147	6	3737.37	-32.1403
7	3671.8	-5.03837	8	3640.95	28.0371	9	3610.09	9.47239
10	3540.67	-16.4918	11	3467.38	-7.76277	12	3409.53	-11.769
13	3343.96	54.4021	14	3286.11	-3.27382	15	3224.4	-68.7559
16	3174.26	4.97477	17	3127.97	-43.1487	18	3089.4	64.0928
19	2996.84	-16.1815	20	2935.13	-18.1521	21	2861.84	13.8509
22	2807.85	8.251	23	2746.14	22.4605	24	2699.85	-0.451009
25	2657.43	-3.94408	26	2618.86	2.59892	27	2553.29	-3.62594
28	2483.87	-18.2625	29	2445.3	-5.60928	30	2360.44	-62.7639
31	2306.45	-45.4356	32	2275.59	-1.43004	33	2194.6	28.8237
34	2098.17	-28.1273	35	2055.75	22.6402	36	2013.32	18.4821
37	1978.61	-11.6826	38	1943.89	18.9006	39	1893.75	6.63239
40	1828.19	48.7539	41	1758.76	-21.0363	42	1720.19	33.3583
43	1673.91	19.2754	44	1643.05	16.1137	45	1600.63	9.93121
46	1554.34	64.0087	47	1488.78	9.17593	48	1446.35	18.3431
49	1346.07	12.8128	50	1319.07	8.72365	51	1238.08	-17.8254
52	1203.36	22.8136	53	1168.65	20.2624	54	1133.94	2.62138
55	1099.23	45.9468	56	1037.52	16.6367	57	987.375	29.4249
58	941.092	53.0574	59	906.379	-4.37765	60	860.096	-2.69474

Fig 8: Infra red spectrum of Glipizide and microcrystalline cellulose

S=O stretch of sulphonamides occurs at 1370-1335 cm^{-1}. In the above spectrum S=O stretch can be noticed at peak number 49 at 1346 cm^{-1}.

C=O stretch of amide occurs at 1673.91.34 cm^{-1}.

Aliphatic CH stretch occurs at 2962 and 2872 cm^{-1}. In the above spectrum the CH stretch can be noticed at peak 20 at 2935 cm^{-1}.



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Resolution	16 cm-1
Zero Filling	ON
Apodization	Cosine
Gain	256
Scanning Speed	2 mm/sec
Date/Time	1/19/2010 11:51AM
Update	1/19/2010 0:14PM
Operator	C.Geetha
File Name	SSG +Glipizide
Sample Name	SSG +Glipizide
Comment	

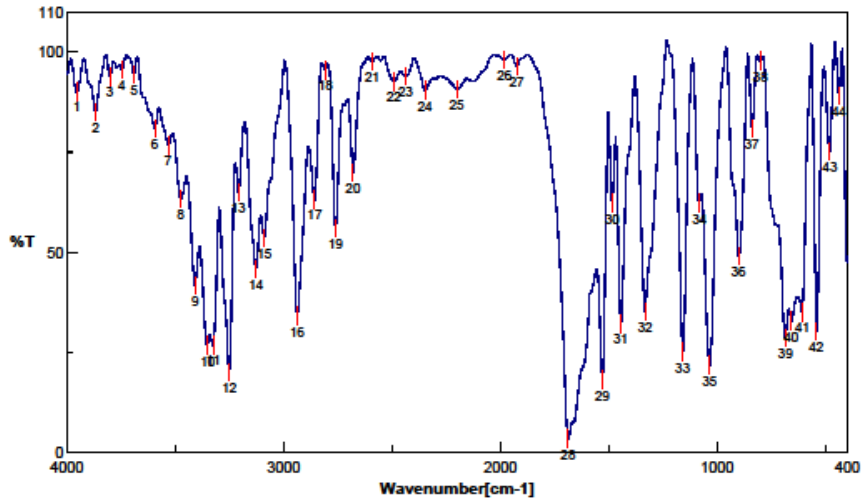
No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3930.22	-11.9048	2	3860.79	-71.7469	3	3818.36	33.273
4	3772.08	-27.4912	5	3741.23	12.416	6	3683.37	-94.0633
7	3633.23	39.6729	8	3598.52	15.5782	9	3563.81	13.8328
10	3517.52	-13.3929	11	3471.24	-2.96947	12	3405.67	17.4358
13	3374.82	12.8095	14	3336.25	27.3339	15	3262.97	-13.6
16	3174.26	-5.01863	17	3104.83	1.26761	18	3070.12	46.5732
19	2996.84	4.85459	20	2962.13	-16.0341	21	2892.7	-34.3449
22	2803.99	-16.5577	23	2749.99	-17.151	24	2692.14	-22.2094
25	2649.71	5.80332	26	2626.57	10.4039	27	2576.43	-29.8526
28	2526.29	-21.7579	29	2491.58	9.67158	30	2437.58	-19.7111
31	2356.59	-31.9407	32	2314.16	-5.7269	33	2183.02	-33.6147
34	2105.89	25.7508	35	2071.17	-7.61469	36	2024.89	-9.73484
37	1978.61	-6.97994	38	1928.47	23.2893	39	1866.76	28.4578
40	1820.47	47.5792	41	1781.9	-5.93363	42	1747.19	11.7711
43	1689.34	49.0766	44	1662.34	50.5104	45	1627.63	2.48124
46	1542.77	36.0643	47	1515.78	45.3083	48	1481.06	22.8109
49	1450.21	18.546	50	1411.64	-12.3665	51	1353.78	10.3023
52	1288.22	8.71235	53	1226.5	17.5401	54	1195.65	-12.1988
55	1145.51	21.0939	56	1099.23	12.8821	57	1052.94	-18.9697
58	1029.8	-29.6024	59	964.233	13.7557	60	914.093	29.9209

Fig 9: Infra red spectrum of Glipizide and Sodium starch glycolate

S=O stretch of sulphonamides occurs at 1370-1335 cm^{-1}. In the above spectrum S=O stretch can be noticed at peak number 51 at 1353 cm^{-1}.

C=O stretch of amide occurs at 1689.34 cm^{-1}.

Aliphatic CH stretch occurs at 2962 and 2872 cm^{-1}. In the above spectrum the CH stretch can be noticed at peak 21 at 2892 cm^{-1}.



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Zero Filling	ON
Apodization	Cosine
Gain	8
Scanning Speed	2 mm/sec
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Update	1/19/2010 0:11PM
Operator	C.Geetha
File Name	Metformin +Glipizide
Sample Name	Metformin +Glipizide
Comment	

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3953.36	90.1227	2	3868.5	85.0701	3	3802.94	93.8796
4	3745.08	95.5571	5	3691.09	94.4356	6	3594.66	80.86
7	3532.95	76.6927	8	3475.1	63.3759	9	3409.53	41.6961
10	3351.68	26.6819	11	3324.68	26.8008	12	3251.4	20.0256
13	3208.97	65.0055	14	3127.97	45.7051	15	3089.4	53.4712
16	2938.98	34.0957	17	2857.99	63.168	18	2807.85	95.5332
19	2761.56	55.9128	20	2680.57	69.8439	21	2591.86	97.7082
22	2491.58	92.6688	23	2437.58	94.097	24	2348.87	90.4566
25	2202.31	90.6982	26	1982.46	98.0877	27	1924.61	96.4779
28	1689.34	3.45423	29	1531.2	18.091	30	1484.92	62.2932
31	1446.35	32.1217	32	1334.5	35.2289	33	1160.94	24.9981
34	1083.8	62.2636	35	1037.52	21.7773	36	902.523	49.0574
37	840.812	80.9956	38	802.242	97.8447	39	686.534	28.6397
40	659.536	32.8698	41	609.396	35.0058	42	543.828	30.2763
43	482.117	75.1949	44	439.69	89.2074			

Fig 10: Infra red spectrum of Glipizide and Metformin

S=O stretch of sulphonamides occurs at 1370-1335 cm^{-1}. In the above spectrum S=O stretch can be noticed at peak number 32 at 1334.5 cm^{-1}.

C=O stretch of amide occurs at 1689.34 cm^{-1}.

Aliphatic CH stretch occurs at 2962 and 2872 cm^{-1}. In the above spectrum the CH stretch can be noticed at peak 16 at 2938 cm^{-1}.

IV. COMPOSITION OF VARIOUS TRIAL FORMULATIONS FOR THE SR LAYER CONTAINING METFORMIN HYDROCHLORIDE

Metformin hydrochloride sustained release formulations with HPMC as rate controlling polymer were prepared by direct compression technique and the composition of the sustained release formulations was given in table 3.

Table 3: Composition of Various Trial Formulations for the SR Layer Containing Metformin hydrochloride

Formulation code	F1	F2	F3
Metformin(mg)	500	500	500
HPMC K100M(mg)	360	-	-
HPMC K15M(mg)	-	360	-
HPMC K4M(mg)	-	-	360
Micro crystalline cellulose(mg)	125	125	125
Silica gel(mg)	5	5	5
Magnesium stearate(mg)	5	5	5
Total weight(mg)	995	995	995

V. EVALUATION OF METFORMIN HYDROCHLORIDE SR TABLETS

a. Weight variation test

In a weight variation test, the pharmacopoeial limit (United States Pharmacopoeia, 2000) for the percentage deviation more than 324mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the uniformity of weight as per official requirements of the United States Pharmacopoeia (2000). The results were shown in table 4.

Table 4: Weight variation of Metformin hydrochloride tablets

S. No.	Formulation code	Weight range of 20 Tablets	Average weight	Limit range (±7.5%)
1	F_1	973-997mg	985.45mg	936.2-1034.7
2	F_2	971-998mg	989mg	939.5-1038.4
3	F_3	975-998mg	988mg	938.6-1037.4

b. Hardness test

Formulated Metformin hydrochloride SR tablets were tested for hardness using Pfizer hardness tester. The results of hardness test were given in table 5.

Table 5: Hardness test of Metformin hydrochloride SR tablets

S. No.	Formulation code	Hardness (kg/cm^2)
1	F_1	7
2	F_2	6.5
3	F_3	5.5

c. Friability

Tablet hardness is not an absolute indicator of strength (Banker & Ander, 1987). Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage of friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits (Banker & Ander, 1987). The results of friability test were given in table 6.

Table 6: Friability test of Metformin hydrochloride SR tablets

S. No.	Formulation code	Friability (%)
1	F_1	0.46
2	F_2	0.59
3	F_3	0.52

b. Drug content Uniformity

Metformin hydrochloride SR tablets are tested for the drug content as prescribed in the USP. Good uniformity in content was found among different formulations and the percentage of drug

content was more than 99%. Percentages of drug present in the tablets were given in the table 7.

Table 7: Drug content test of Metformin hydrochloride SR tablets

S. No.	Formulation code	Amount of Metformin hydrochloride	
		Amount in mg	Amount in percentage
1	F_1	500	100
2	F_2	496	99.2
3	F_3	501	100.2

c. Disintegration Test

Disintegration test was carried out for formulated Metformin hydrochloride SR tablets using the disintegration test apparatus as prescribed in USP. The results of the disintegration test were given in table 8.

Table 8: Disintegration test of Metformin Hydrochloride SR tablets

S. No.	Formulation code	Disintegration Time
1	F_1	35min
2	F_2	28 min
3	F_3	20 min

d. *In vitro* Dissolution Study

Figure 11 shows the dissolution profile of the prepared Metformin hydrochloride formulations. All three dissolution profiles appear to be similar.

Metformin HCl is highly soluble in water with poor inherent compressibility. Moreover its high dose (500mg) poses a significant challenge for developing an SR dosage form. For obtaining a desirable drug release profile, cost effectiveness, and broader regulatory acceptance, HPMC was chosen as the release-controlling polymer. HPMC is a mixed alkyl hydroxyalkyl cellulose ether containing methoxyl hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents. Specifically the hydration rate of HPMC increases with an increase in the hydroxypropyl content and the solubility of HPMC is pH independent (Hogan, 1989).

The molecular weight of the HPMC polymer in a matrix tablet, and thereof apparent viscosity of the hydrated polymer, is important in determining the drug-release properties. It is generally accepted that drug dissolution from tablets is slower for higher viscosity grades of HPMC polymers. However, in this study similar Metformin release rates were observed for tablets containing 36% of HPMC.

The mechanism of the drug release in these formulations is mainly governed by diffusion and as the drug is so highly soluble, polymer viscosity grade did not significantly affect the diffusion rate.

In general, slower release may be achieved with higher polymer levels or higher viscosity grade of HPMC in the formulation. This is mainly due to the longer period of time required to reach the disentanglement concentration at the tablet surface, which in turn equates to the greater resistance to surface erosion, Such phenomenon is more significant in the gastro-intestinal tract where attrition on the hydrated surface of the matrix is greater. This is because drug release does not result solely from active diffusion through the hydrated polymer, but also from polymer erosion leading to a thinner hydrated gel layer i.e. short diffusional path for drug release.

i. Release profile of Metformin from Metformin hydrochloride SR Tablets

The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermined manner. According to the theoretical release pattern, a once daily Metformin SR formulation should release 175.6 mg in one hour and 46.3 mg per hour for up to 8 hours (Mutalik & Hiremath, 2000). All the formulations showed the burst release of Metformin in the initial hours, which is probably due to faster dissolution of highly water-soluble drug from the core and its diffusion out of the matrix, forming the pores for the entry of solvent molecule.

Table 9: *In vitro* Dissolution test of Metformin SR tablets

Time(hrs)	Percentage Release	Percentage Release F_2	Percentage Release F_3

	F_1		
1	35.3	36.4	43.7
2	44	46.08	48.6
3	53.4	55.48	56.86
4	61.6	64.2	64.66
5	69.4	72.9	74.75
6	78.4	81.6	84.3
7	83.9	88.9	91.03
8	92.8	96.3	98.14
9	96.5	99.5	100
10	99.5	-	-

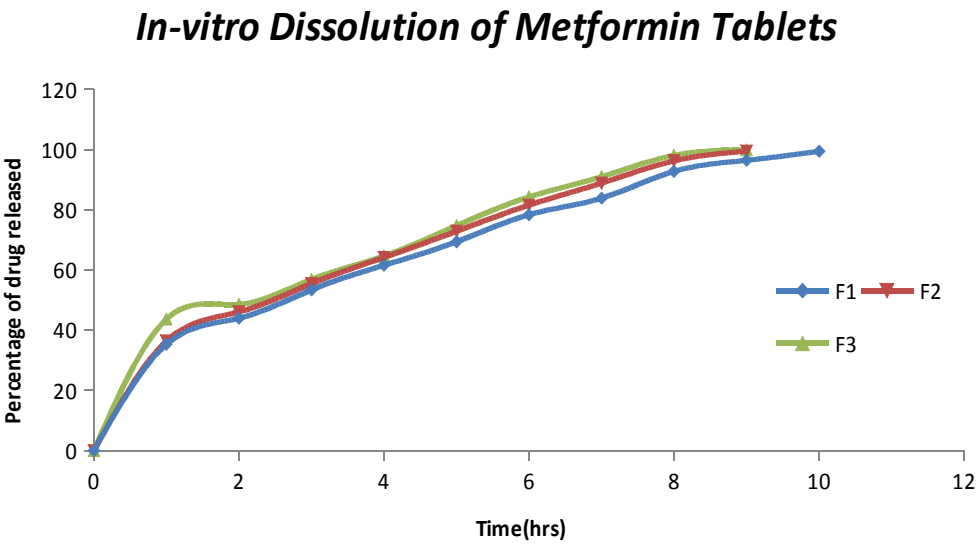

Fig 11: *In vitro* Dissolution study of Metformin hydrochloride SR tablets

ii. Drug Release Kinetics

To know the mechanism of drug release from these formulations, the data were treated according to first order (log cumulative percentage of drug released versus time), Higuchi's (cumulative percentage of drug released versus square root of time; 1962), and Korsemeyer's (log cumulative percentage of drug released versus log time 1983) equations along with a zero-order (cumulative percentage of drug release versus time) pattern. In table 10, the kinetic parameters for Metformin HCl release from the HPMC matrix tablets were presented. As clearly indicated in table 10, the formulations did not follow zero-order or first-order release patterns.

The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation. Release of drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid, depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics or Higuchi's kinetics. To confirm the diffusion mechanism, the data were fitted into Korsemeyer's equation (Korsemeyer et al., 1983). For matrix tablets, as n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism (Fassihi & Ritschel, 1993; Peppas, 1985).

All the formulations showed good linearity (R^2: 0.974 to 0.992), indicating that the diffusion is the dominant mechanism of drug release from these formulations.

Table 10: Drug release kinetics of Metformin hydrochloride Sustained Release tablets

Formulation Code	Zero order R^2	First order R^2	Higuchi's kinetics R^2	Korsemeyer's kinetics R^2
F_1	0.9225	0.826	0.9926	0.9886
F_2	0.989	0.8076	0.9928	0.989
F_3	0.8997	0.8305	0.9747	0.9528

Dissolution kinetics of formulation F_1

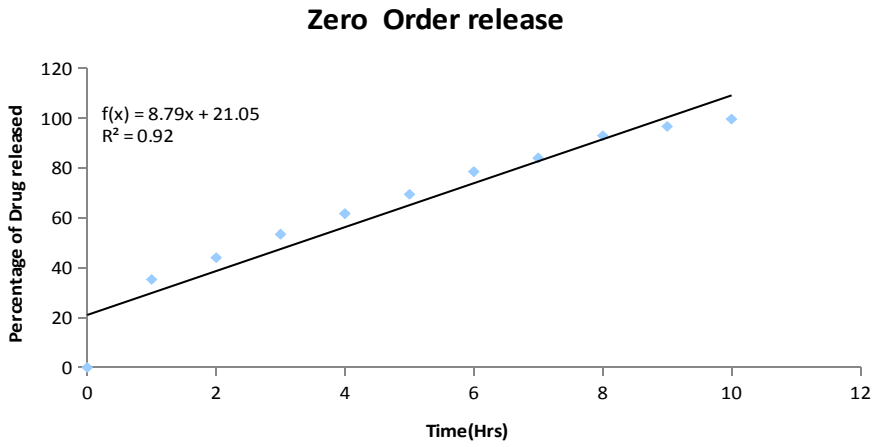

Fig12: Zero order release of Metformin hydrochloride SR tablets F_1

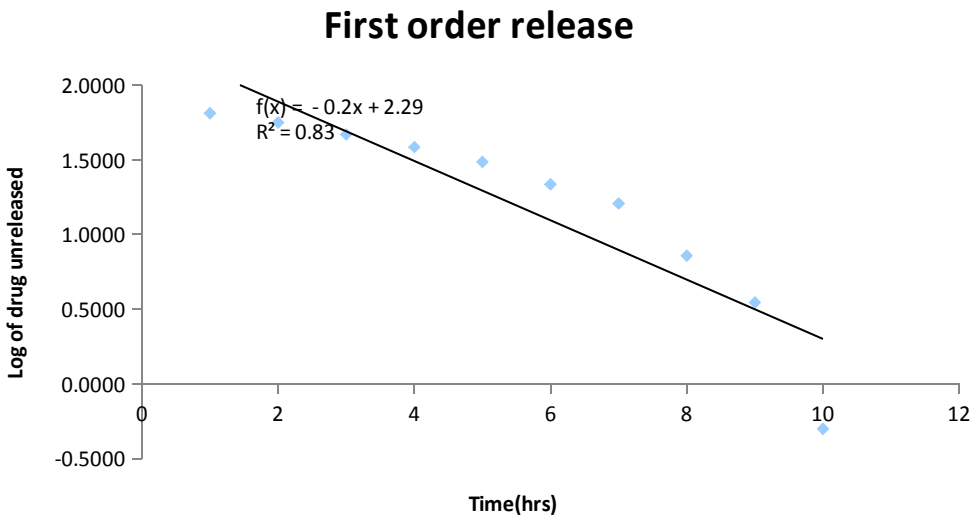

Fig13: First order release of Metformin hydrochloride SR tablets F_1

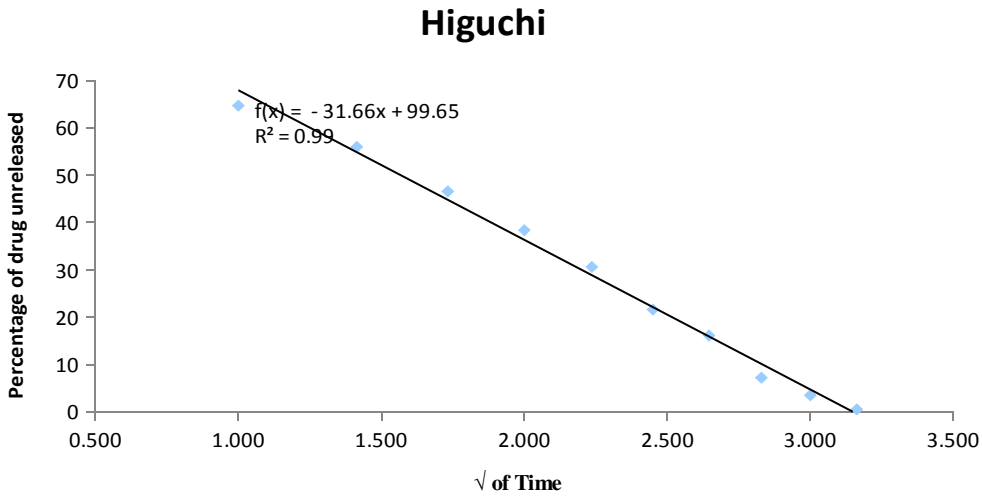

Fig14: Higuchi's kinetics of Metformin hydrochloride SR tablets F_1

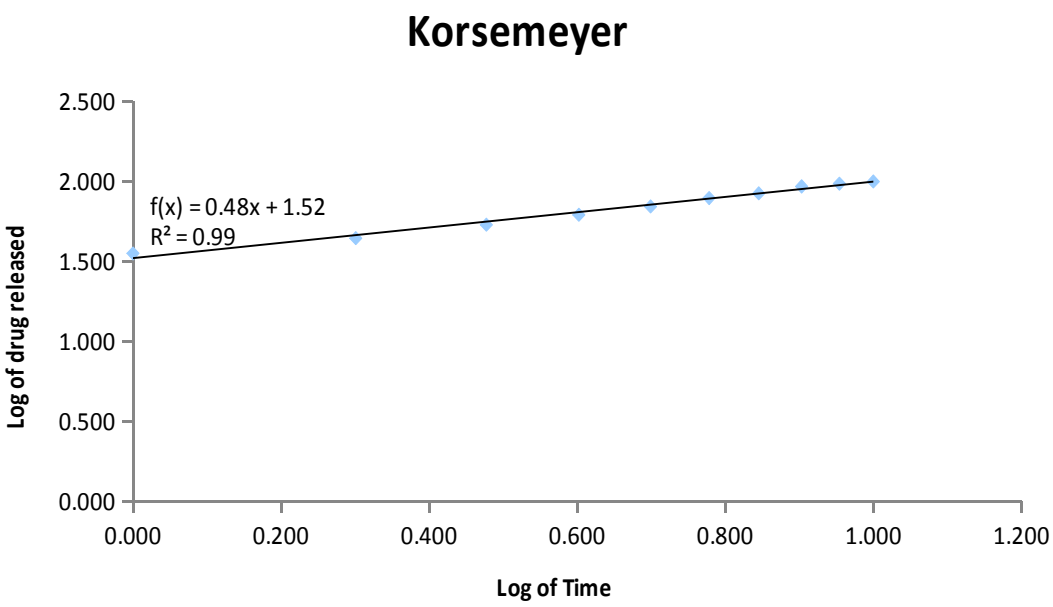

Fig15: Korsemeyer's kinetics of Metformin hydrochloride SR tablets F_1

Dissolution kinetics of formulation F_2

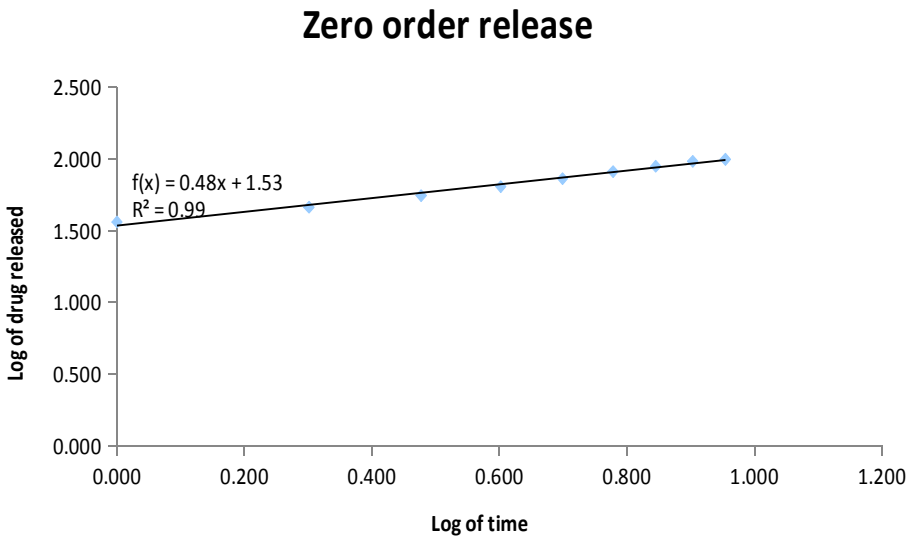

Fig 16: Zero order release of Metformin hydrochloride SR tablets F_2

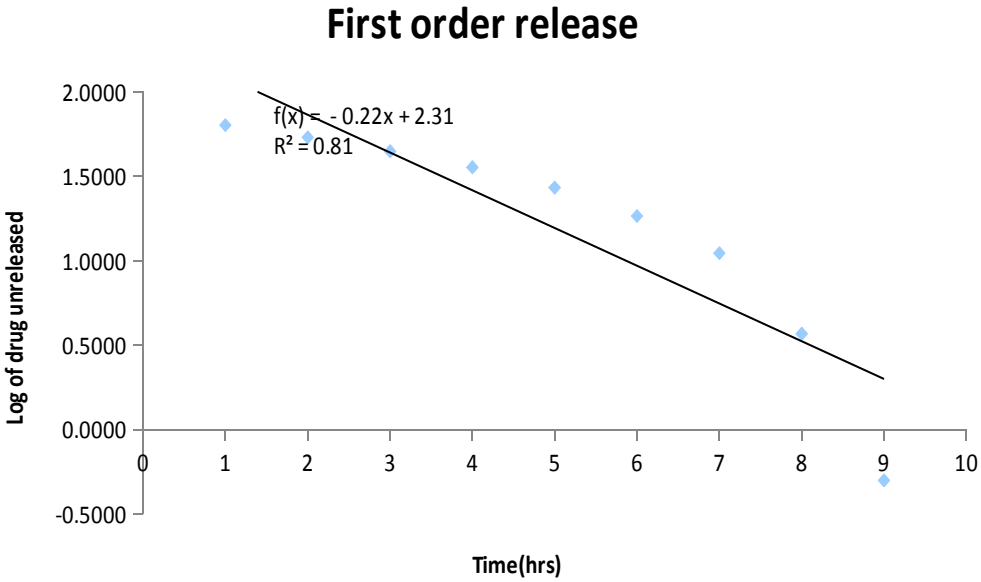

Fig 17: First order release of Metformin

hydrochloride SR tablets F_2

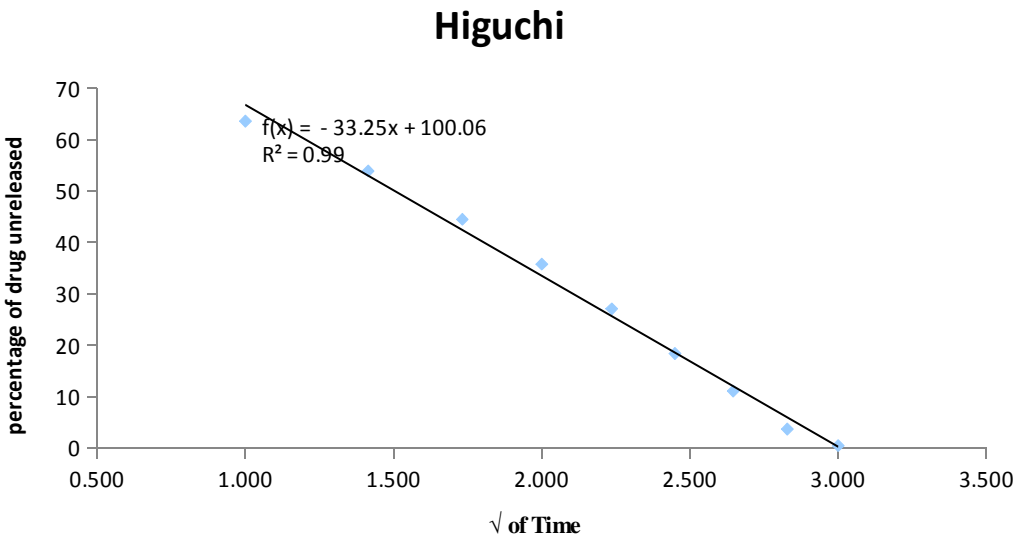

Fig18: Higuchi's kinetics of Metformin hydrochloride SR tablets F_2

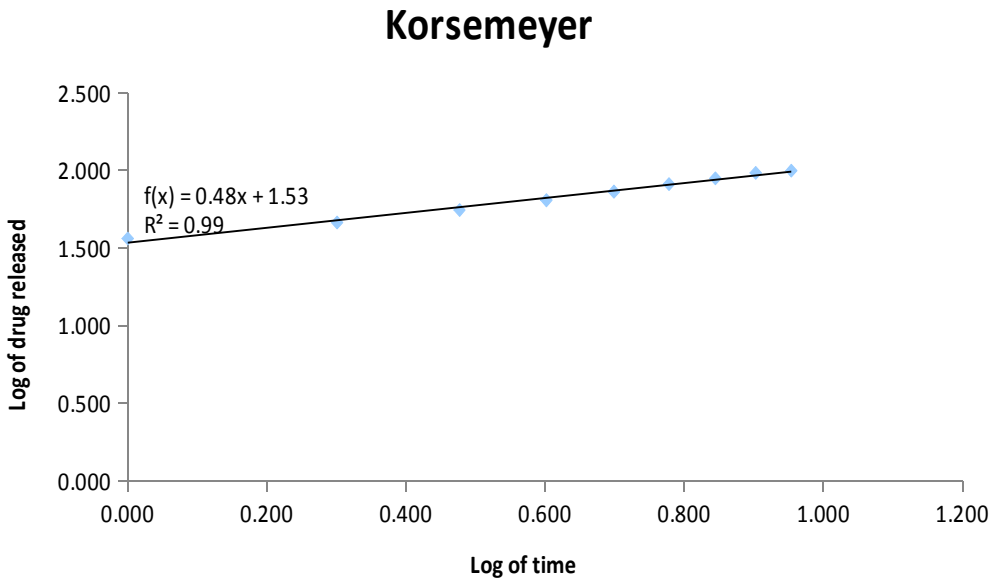

Fig19: Korsemeyer's kinetics of Metformin hydrochloride SR tablets

Dissolution kinetics of formulation F_3

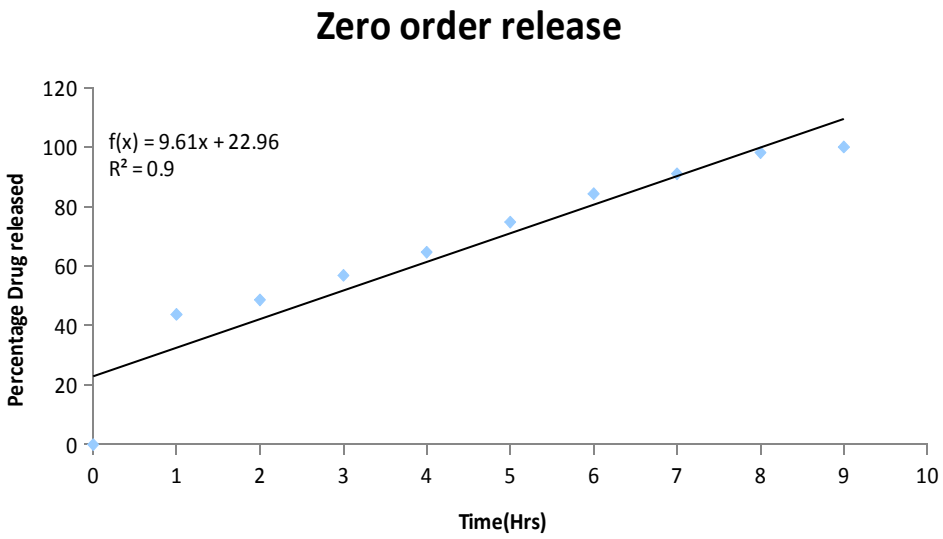

Fig20: Zero order release of Metformin hydrochloride SR tablets F_3

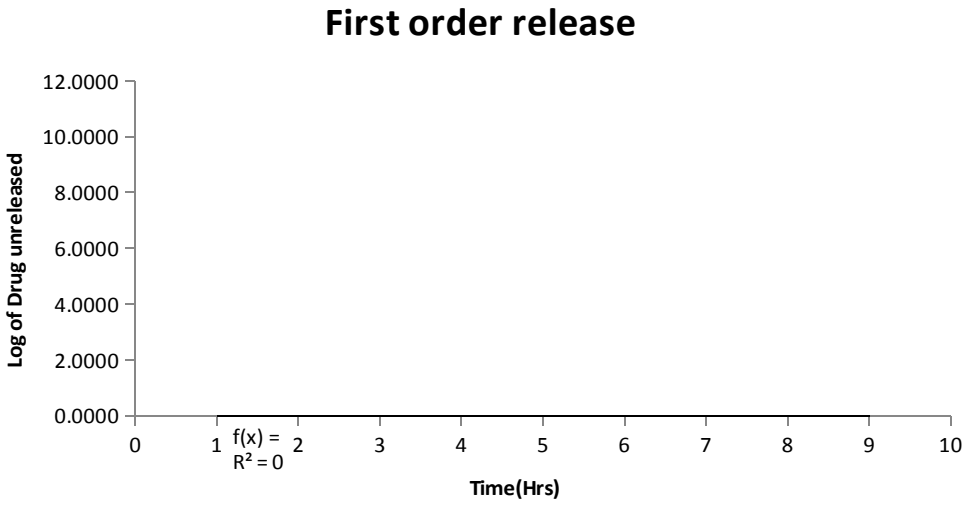

Fig21: First order release of Metformin hydrochloride SR tablets F_3

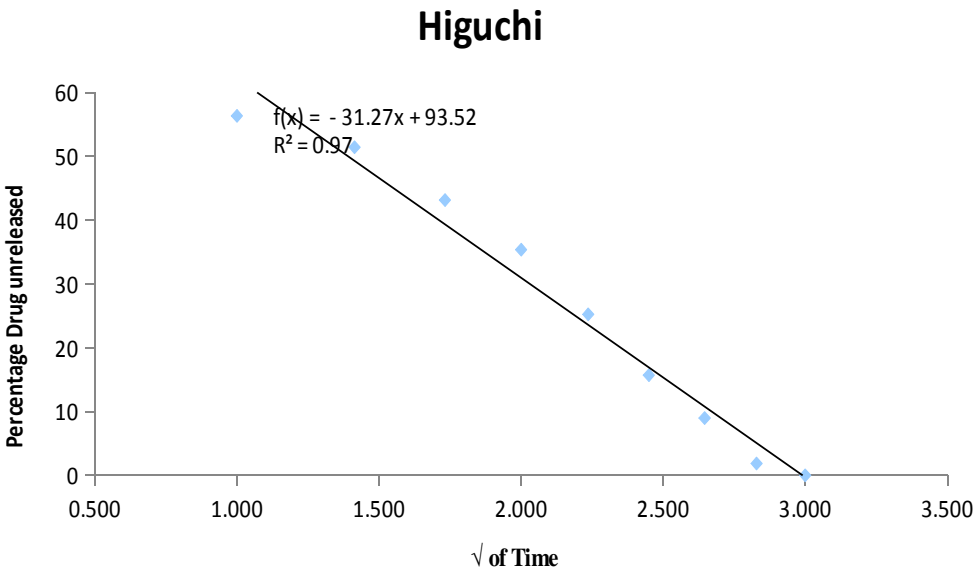

Fig22: Higuchi's kinetics of Metformin hydrochloride SR tablets F_3

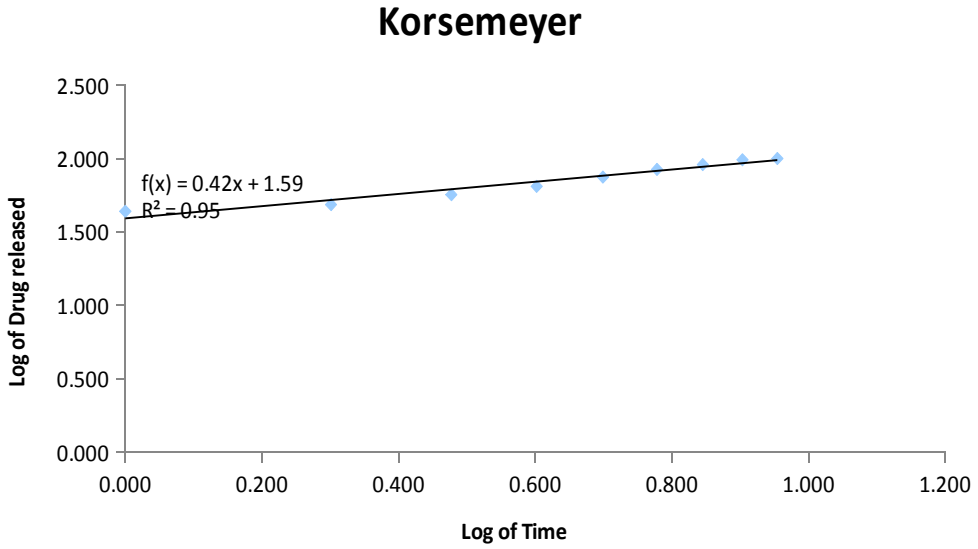

Fig23: Korsemeyer's kinetics of Metformin hydrochloride SR tablets F_3

VI. COMPOSITION OF VARIOUS TRIAL FORMULATIONS FOR THE IR LAYER CONTAINING GLIPIZIDE

Glipizide immediate release tablets formulations were prepared using kneading method of solid dispersion technique using sodium starch glycolate as the disintegrant and drug carrier. The composition of the immediate release formulations is given in table 11.

Table 11: Composition of Various Trial Formulations for the IR Layer Containing Glipizide

Formulation code	F4	F5	F6
Drug (mg)	5	5	5
Sodium Starch Glycolate(mg)	10	20	40
Microcrystalline cellulose(mg)	82	72	52
Talc(mg)	2	2	2
Tartrazine(mg)	1	1	1
Total weight(mg)	100	100	100

VII. EVALUATION OF GLIPIZIDE IR TABLETS

a. Weight variation test

In a weight variation test, the pharmacopoeial limit (United States Pharmacopoeia, 2000) for the percentage deviation more than 80mg is ± 7.5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the uniformity of weight as per official requirements of the United States Pharmacopoeia (2000). The results were shown in table 12.

Table 12: Weight variation of Glipizide tablets

S. No.	Formulation code	Weight range of 20 Tablets (mg)	Average weight (mg)	Limit range (±7.5%)
1	F_4	92-97	95	87.88 -102
2	F_5	91-97	96	88.8-103.2
3	F_6	92-96	95	87.88 -102

b. Hardness test

Formulated Glipizide IR tablets were tested for hardness using Pfizer hardness tester. The results of hardness test were given in table 13.

Table 13: Hardness test of Glipizide IR tablets

S. No.	Formulation code	Hardness (kg/cm^2)
1	F_4	4
2	F_5	3.8
3	F_6	3.8

c. Friability

Tablet hardness is not an absolute indicator of strength (Banker & Ander, 1987). Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage of friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits (Banker & Ander, 1987). The results of friability test were given in table 14.

Table 14: Friability test of Glipizide IR tablets

S. No.	Formulation code	Friability (%)
1	F_4	0.48
2	F_5	0.63
3	F_6	0.57

d. Drug content Uniformity

Glipizide IR tablets are tested for the drug content as prescribed in the USP. Good uniformity in content was found among different formulations and the percentage of drug content was more than 99%. Percentages of drug present in the tablets were given in the table 15.

Table 15: Drug content test of Glipizide IR tablets

S. No.	Formulation code	Amount of Glipizide	
		Amount in mg	Amount in percentage
1	F_4	4.98	99.6
2	F_5	5.15	103
3	F_6	5.1	102

e. Disintegration Test

Disintegration test was carried out for formulated Glipizide IR tablets using the disintegration test apparatus as prescribed in USP. The results of the disintegration test were given in table 16.

Table 16: Disintegration test of Glipizide IR tablets

S. No.	Formulation code	Disintegration Time
1	F_4	40 sec
2	F_5	28 sec
3	F_6	15 sec

f. *In vitro* Dissolution Study

The release of glipizide from the tablets was studied in 900 ml of dissolution medium using a USP dissolution paddle assembly (Lab India Disso 2000) instrument at 50 rpm and 37±0.5C. The dissolution medium used was phosphate buffer (pH 6.8)

Samples of dissolution medium were withdrawn at suitable time interval and was then determined spectrophotometrically at 276 nm. Graph was plotted with time vs percentage drug released.

Percentage release of Glipizide from the formulations F_4 and F_5 are given in table17 and percentage release of Glipizide from formulation F_6 is given in table 18.

Table 17: *In vitro* Dissolution test of Glipizide IR tablets (F_4& F_5)

S. No	Time(min)	Percentage Release from F_4	Percentage Release from F_5
1	5	52.8	75.8
2	10	64.2	85.6
3	15	81	101
4	20	99.6	-

Table 18: *In vitro* Dissolution test of Glipizide IR tablets (F_6)

S. No	Time(min)	Percentage Release from F_6
1	2	46.72
2	4	62.8
3	6	73.4
4	8	88.8
5	10	100.2

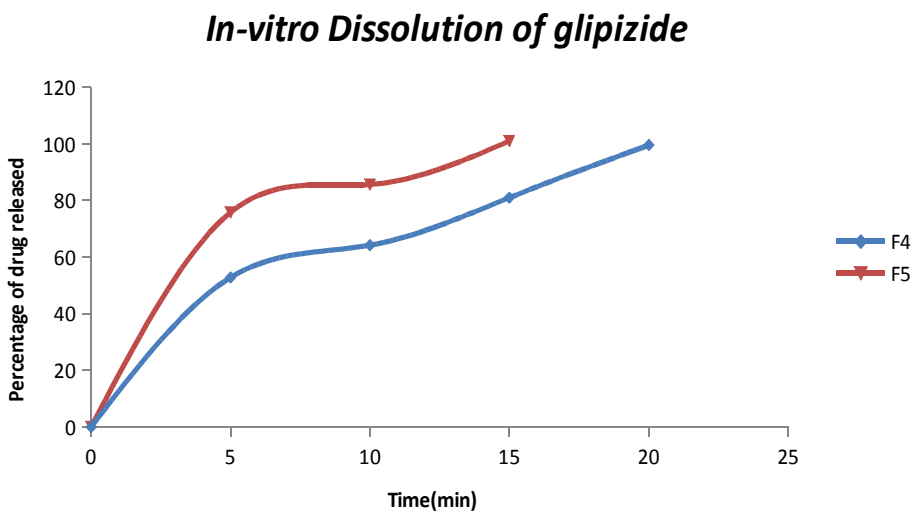

Fig24: *In vitro* Dissolution study of Glipizide IR tablets (F_4 & F_5)

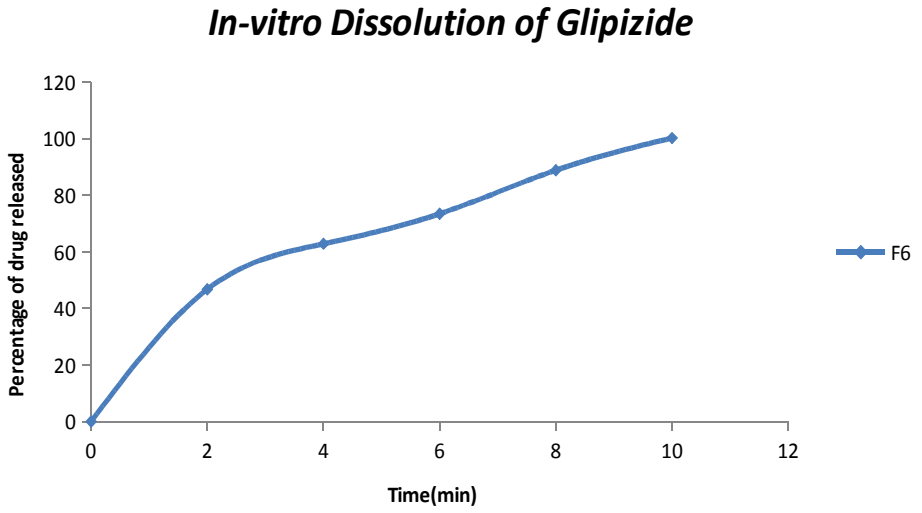

Fig25: *In vitro* Dissolution study of Glipizide IR tablets (F_6)

a. Drug Release Kinetics

To know the mechanism of drug release from these formulations, the data were treated according to first order (log cumulative percentage of drug released versus time), Higuchi's (cumulative percentage of drug released versus square root of time; 1962), and Korsemeyer's (log cumulative percentage of drug released versus log time 1983) equations along with a zero-order (cumulative percentage of drug release versus time) pattern. In table 19, the kinetic parameters for Glipizide release from the immediate release tablets are presented. . As clearly indicated in table 19, the formulations did not follow zero-order or first-order release patterns. The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation and Korsemeyer's equation. The optimized formulation F_4 can be best expressed by Higuchi's equation

Table 19: Drug release kinetics of Glipizide IR tablets

Formulation Code	Zero order R^2	First order R^2	Higuchi's kinetics R^2	Korsemeyer's kinetics R^2
F_4	0.9108	0.755	0.9591	0.9532
F_5	0.7302	0.859	0.9447	0.9561
F_6	0.9102	0.8238	0.9905	0.9908

Dissolution kinetics of formulation F_4

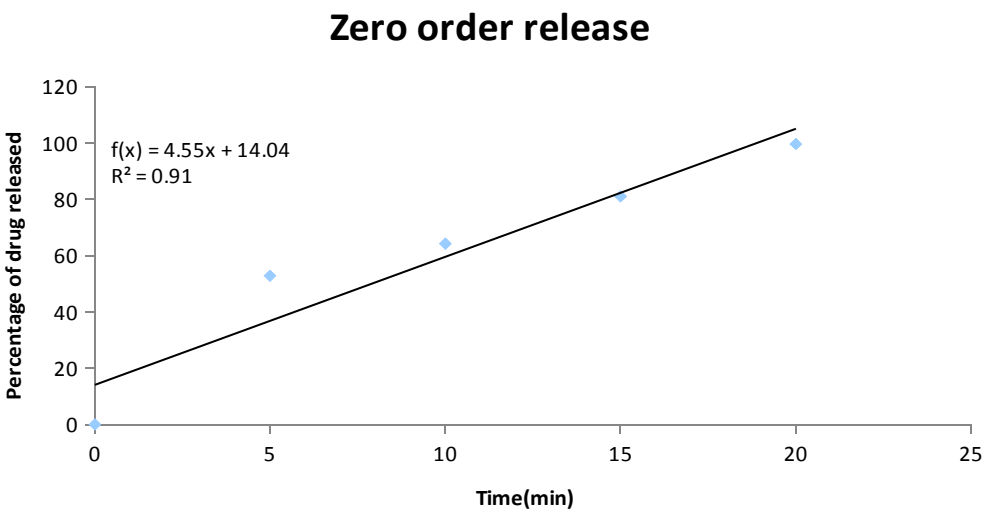

Fig26: Zero order release of Glipizide IR tablets F_4

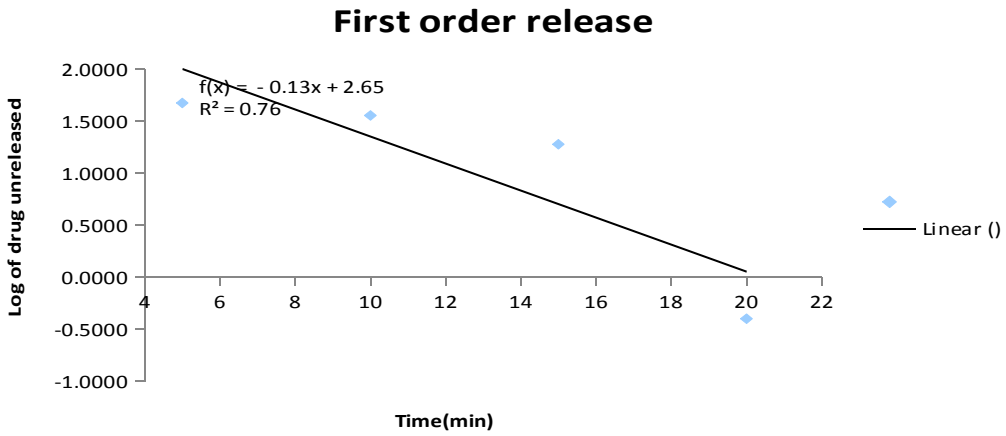

Fig27: First order release of Glipizide IR tablets F_4

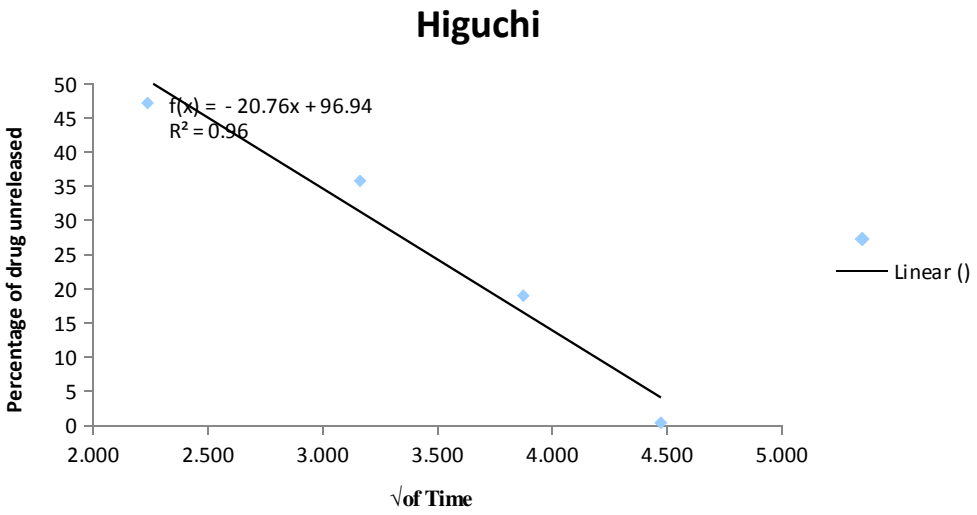

Fig28: Higuchi's kinetics of Glipizide IR tablets F_4

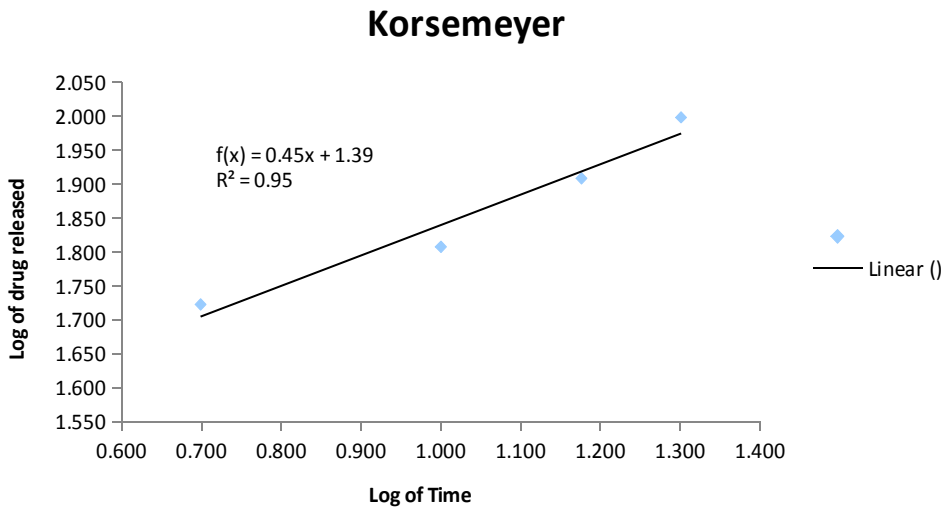

Fig29: Korsemeyer's kinetics of Glipizide IR tablets F_4

Dissolution kinetics of formulation F_5

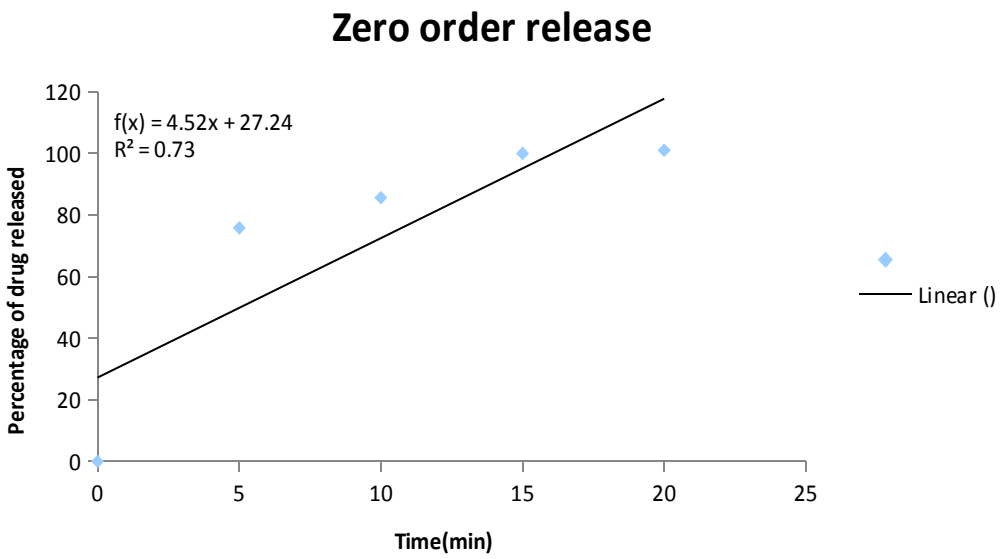

Fig30: Zero order release of Glipizide IR tablets F_5

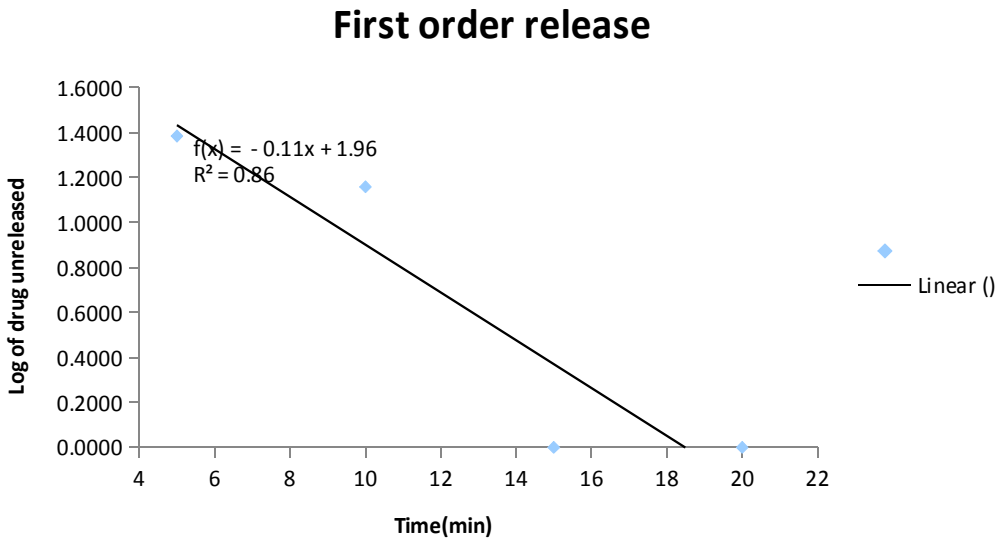

Fig31: First order release of Glipizide IR tablets F_5

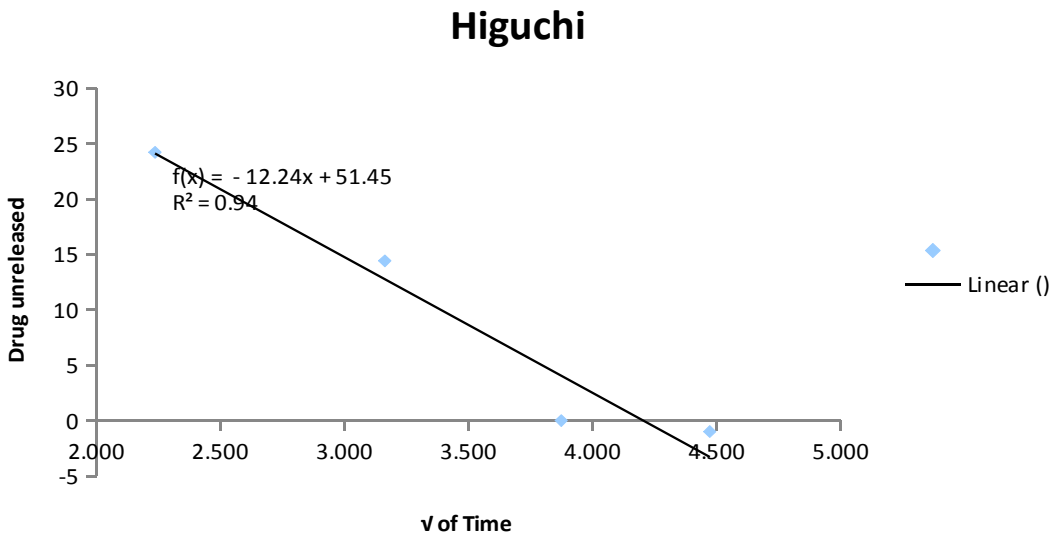

Fig32: Higuchi's kinetics of Glipizide IR tablets F_5

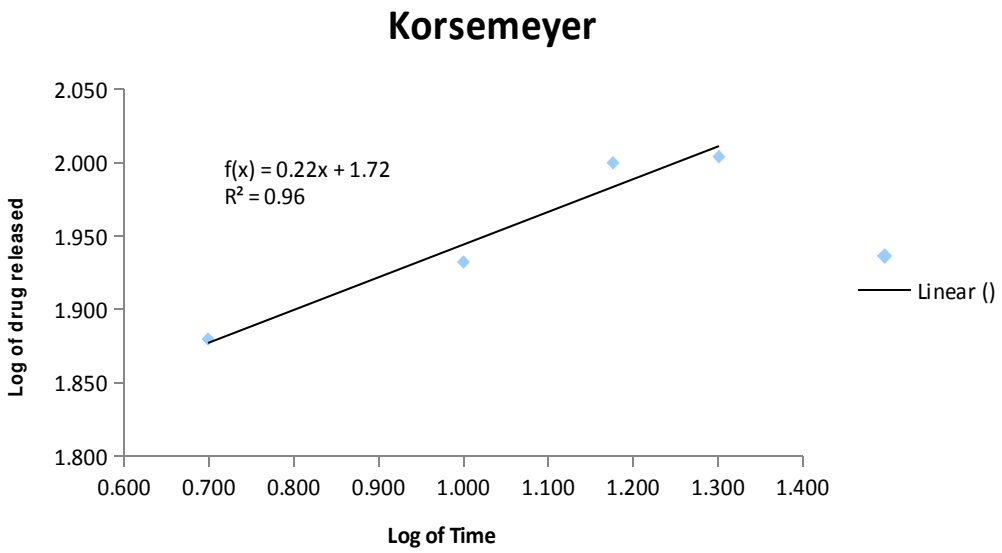

Fig33: Korsemeyer's kinetics of Glipizide IR tablets F_5

Dissolution kinetics of formulation F_6

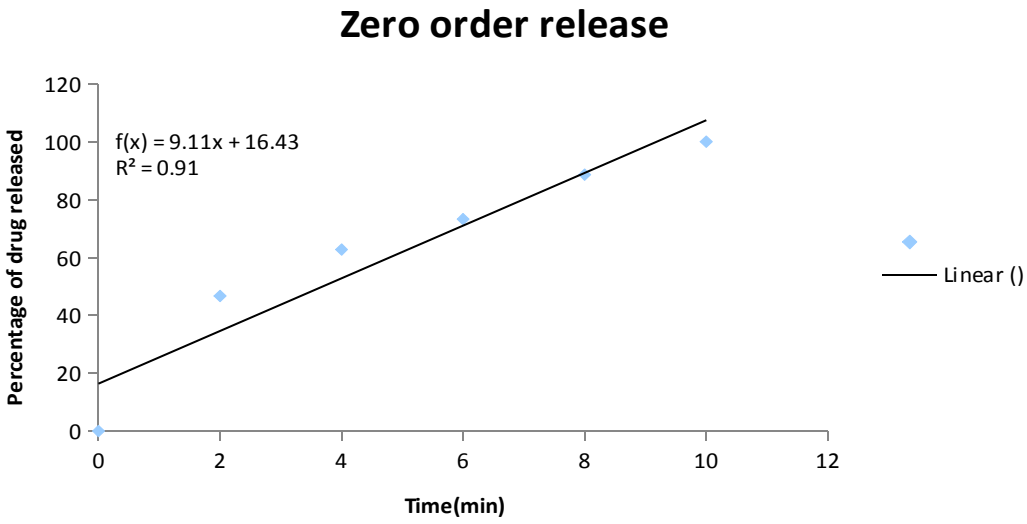

Fig34: Zero order release of Glipizide IR tablets F_6

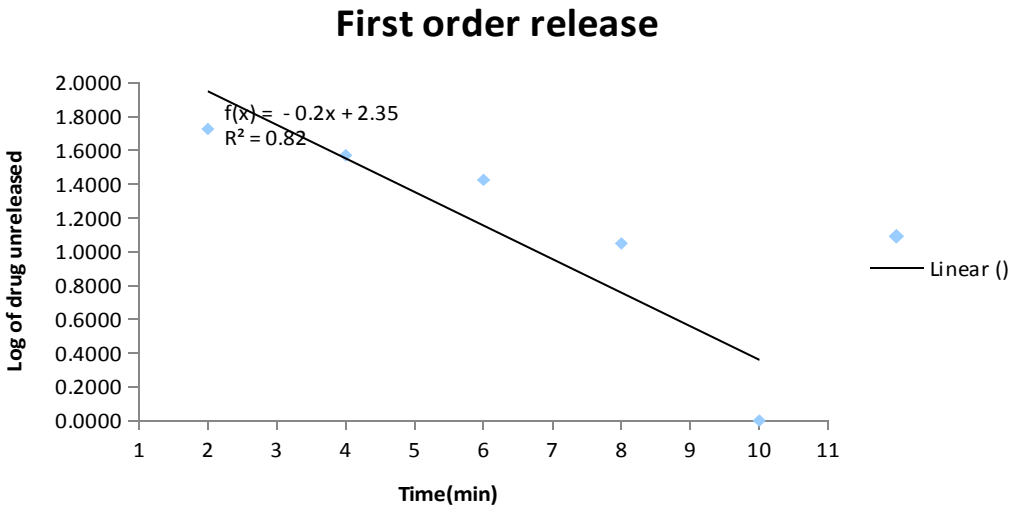

Fig35: First order release of Glipizide IR tablets F_6

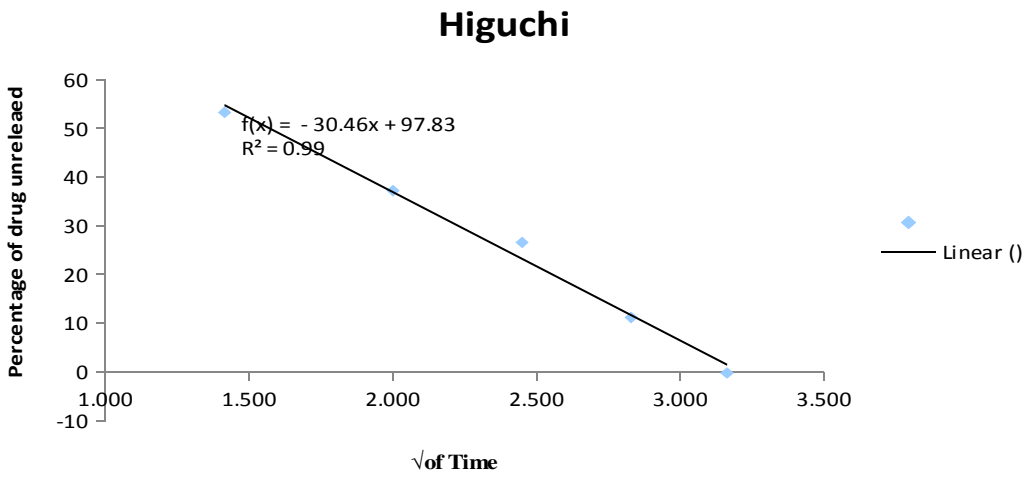

Fig36: Higuchi's kinetics of Glipizide IR tablets F_6

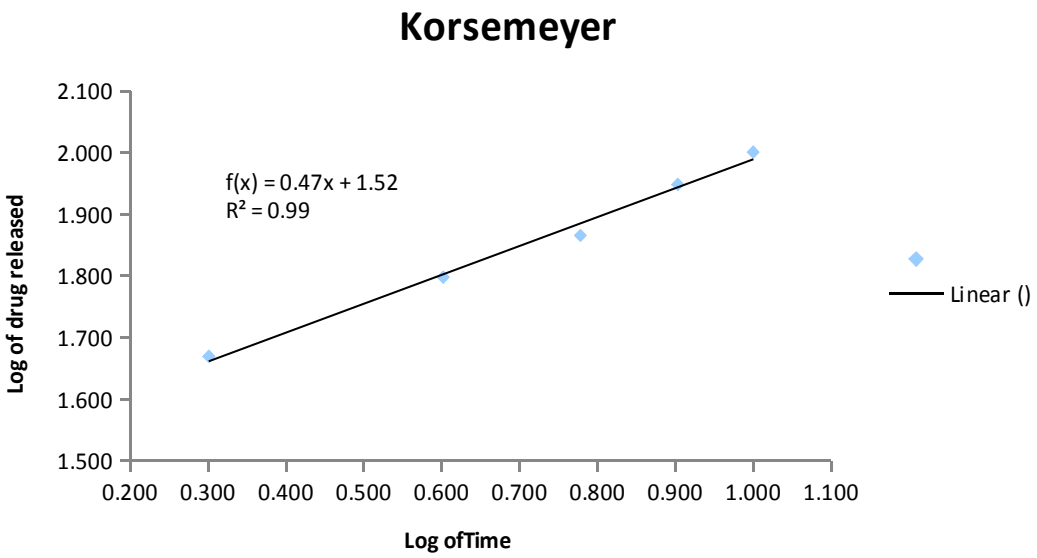

Fig37: Korsemeyer's kinetics of Glipizide IR tablets F_6

VIII. COMPOSITION OF BILAYER TABLET OF METFORMIN HYDROCHLORIDE (SR) AND GLIPIZIDE (IR)

Final bilayer tablets were prepared using optimized formulations of Metformin hydrochloride (F_1) and Glipizide (F_4) to get the bilayer formulation F_7. Composition of bilayer tablet containing Metformin hydrochloride (SR) F_1 and Glipizide (IR) F_4 is given in table 3 and table 11 respectively.

IX. EVALUATION OF BILAYER TABLET CONTAINING METFORMIN HYDROCHLORIDE (SR) AND GLIPIZIDE (IR) TABLETS

a. Weight variation test

In a weight variation test, the pharmacopoeial limit (United States Pharmacopoeia, 2000) for the percentage deviation more than 324mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the uniformity of weight as per official requirements of the United States Pharmacopoeia (2000). The results were shown in table 20.

Table 20: Weight variation of Metformin hydrochloride tablets and Glipizide Bilayer tablets

S. No.	Formulation code	Weight range of 20 Tablets	Average weight	Limit range (±7.5%)
1	F_7	1030-1052	1045mg	992.7-1097.2

b. Hardness test

Formulated Metformin hydrochloride SR tablets were tested for hardness using Pfizer hardness tester. The results of hardness test were given in table 21.

Table 21: Hardness test of Bilayer Tablet containing Metformin hydrochloride (SR) and Glipizide (IR).

S. No.	Formulation code	Hardness (kg/cm^2)
1	F_7	6.5

c. Friability

Tablet hardness is not an absolute indicator of strength (Banker & Ander, 1987). Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage of friability for the bilayer formulation was below 1%, indicating that the friability was within the prescribed limits (Banker & Ander, 1987). The results of friability test were given in table 22.

Table 22: Friability test of Metformin hydrochloride (SR) and Glipizide (IR) tablets

S. No.	Formulation code	Friability (%)

1	F_7	0.46

d. *In vitro* Dissolution Study

The release of Metformin hydrochloride and glipizide from the bilayer tablets was studied in 900 ml of dissolution medium using a USP dissolution paddle assembly (Lab India Disso 2000) instrument at 50 rpm and 37±0.5°C. The dissolution medium used was phosphate buffer (pH 6.8)

Samples of dissolution medium were withdrawn at suitable time interval and was then determined spectrophotometrically at 233nm and276 nm respectively. Graph was plotted with time vs percentage drug released. Percentage release of Metformin from the formulation F_7 was given in table 23 and percentage release of Glipizide from formulation F_7 was given in table 24.

Table 23: *In vitro* Dissolution test of Metformin from bilayer tablets

S. No	Time(hrs)	Percentage Release of Metformin
1	1	35.3
2	2	44
3	3	53.4
4	4	61.6
5	5	69.4
6	6	78.4

7	7	83.9
8	8	92.8
9	9	96.5
10	10	99.5

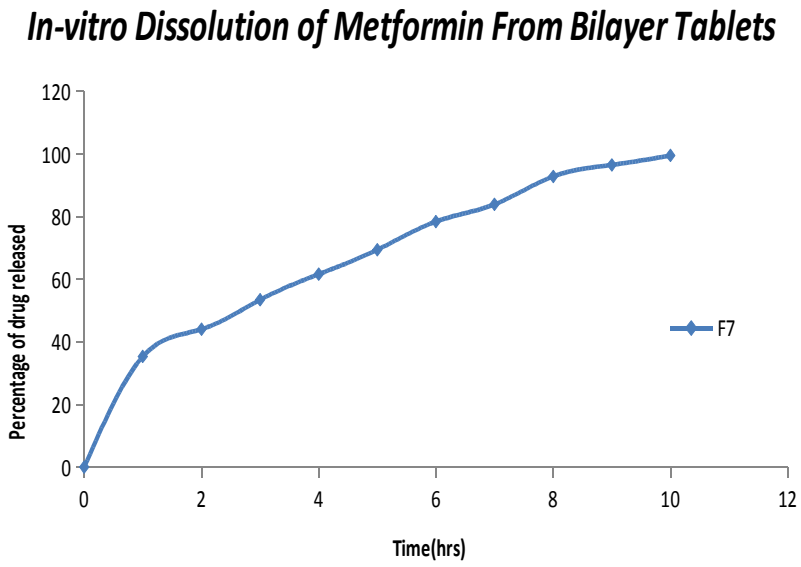

Fig 38: *In vitro* Dissolution study of Metformin hydrochloride From Bilayer tablets

Table 24: *In vitro* Dissolution test of Glipizide from bilayer tablets

S. No	Time(min)	Percentage Release of glipizide
1	5	52.8
2	10	64.2
3	15	81

4	20	99.6

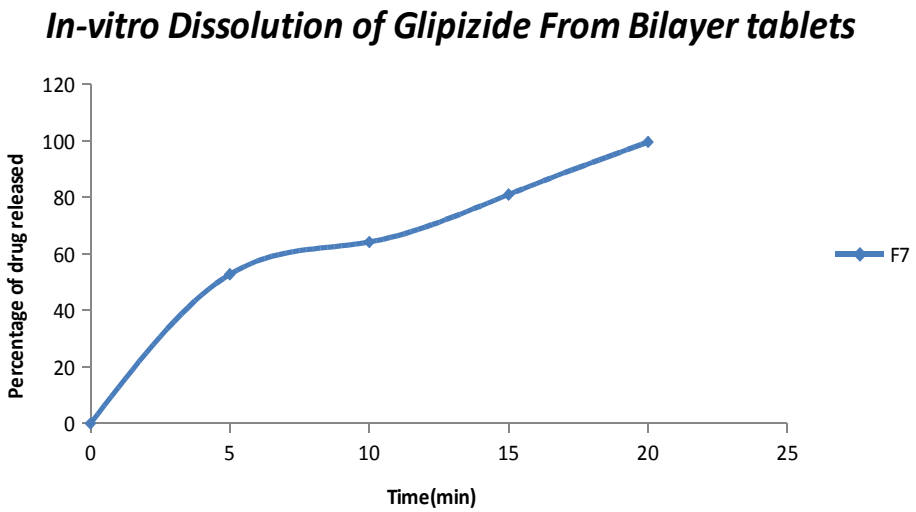

Fig 39: *In vitro* Dissolution study of Glipizide from Bilayer tablets

ii. Drug Release Kinetics

To know the mechanism of drugs released from the formulation, the data were treated according to first order (log cumulative percentage of drug released versus time), Higuchi's (cumulative percentage of drug released versus square root of time; 1962), and Korsemeyer's (log cumulative percentage of drug released versus log time 1983) equations along with a zero-order (cumulative percentage of drug release versus time) pattern. In table 10, the kinetic parameters for Metformin HCl and Glipizide release from the Bilayer tablets were presented. As clearly indicated in table 10, the formulations did not follow zero-order or first-order release patterns.

The in vitro release profiles of both drugs from the formulation could be best expressed by Higuchi's equation. Release of drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid, depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics or Higuchi's kinetics. To confirm the diffusion mechanism, the data were fitted into Korsemeyer's equation (Korsemeyer et al., 1983). For matrix tablets, as n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism (Fassihi & Ritschel, 1993; Peppas, 1985).

The formulation showed good linearity (R^2: 0.959 to 0.992), indicating that the diffusion is the dominant mechanism of drug release from this formulation.

Table 25: Drug release kinetics of Metformin hydrochloride Sustained Release tablets

Formulation F_7	Zero order R^2	First order R^2	Higuchi's Plot R^2	Korsemeyer's plot R^2
Metformin Hydrochloride	0.9225	0.826	0.9926	0.9886
Glipizide	0.9108	0.755	0.9591	0.9532

Dissolution kinetics of Metformin hydrochloride from formulation F_7

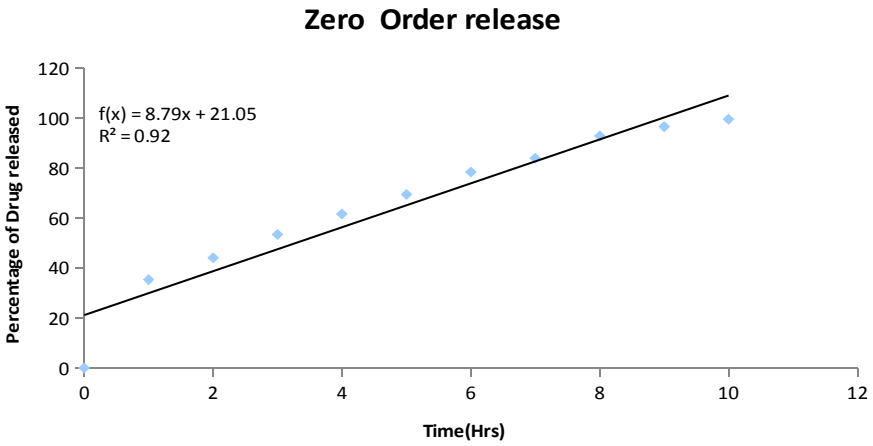

Fig40: Zero order release of Metformin hydrochloride SR from bilayer tablets F_7

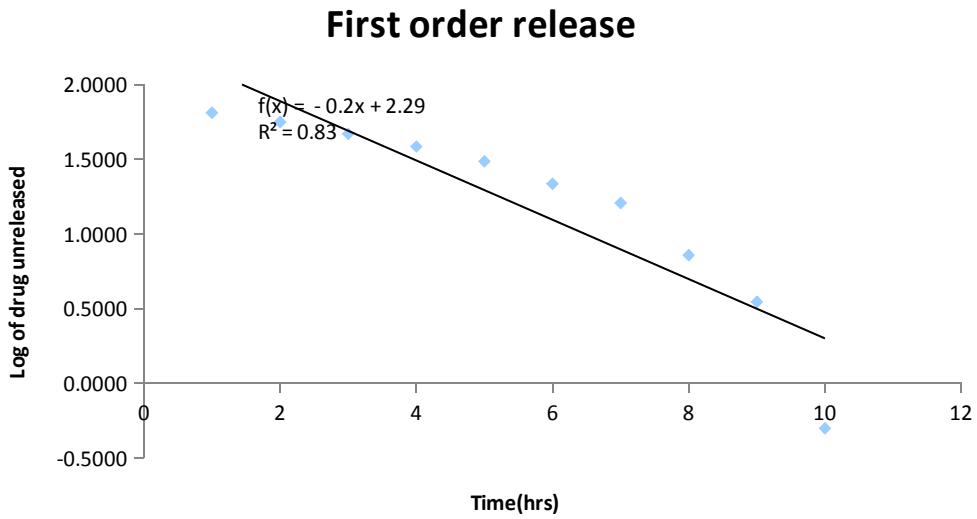

Fig41: First order release of Metformin hydrochloride SR from bilayer tablets F_7

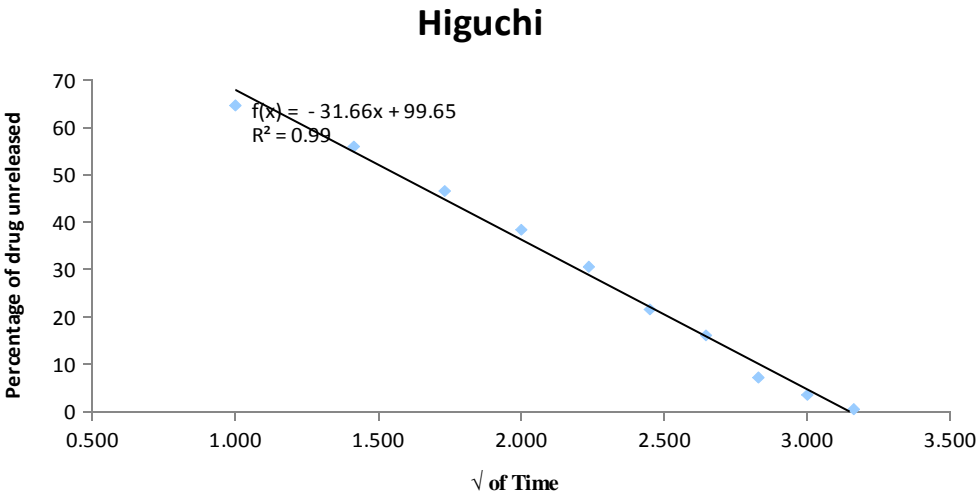

Fig42: Higuchi's kinetics of Metformin hydrochloride SR from bilayer tablets F_7

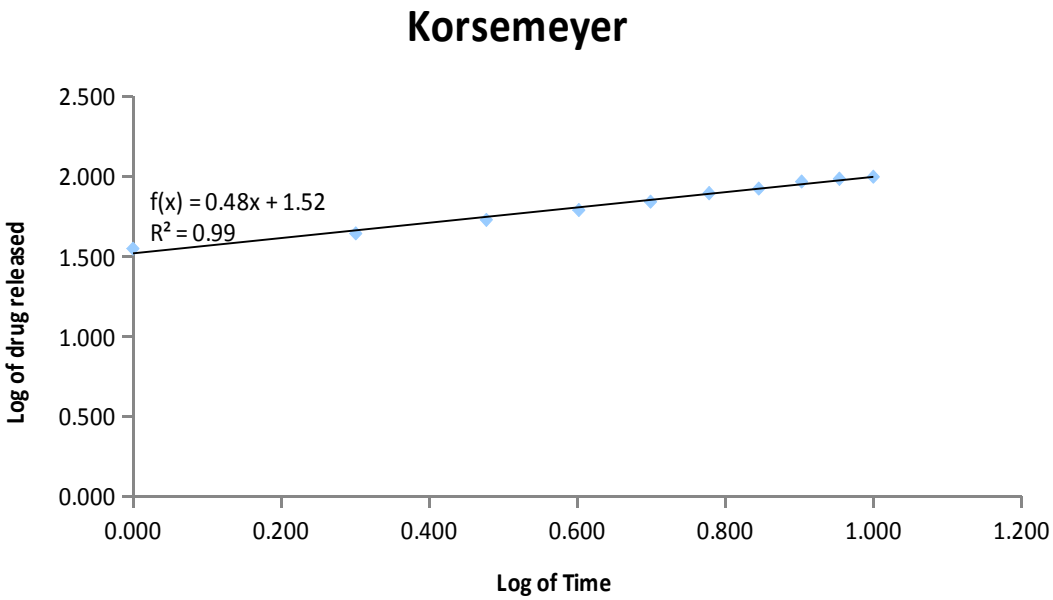

Fig43: Korsemeyer's kinetics of Metformin hydrochloride SR from bilayer tablets F_7

Dissolution kinetics of Glipizide from formulation F_7

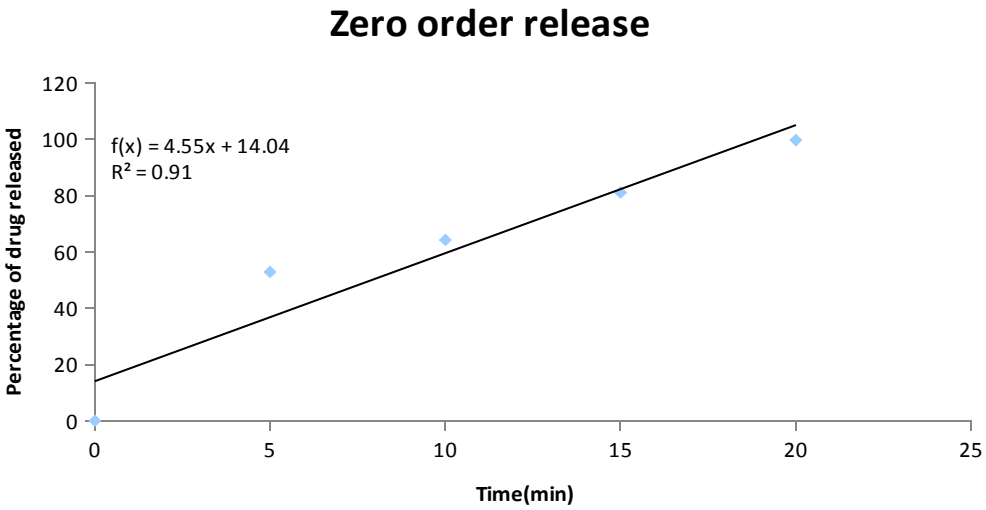

Fig44: Zero order release of Glipizide IR from bilayer tablets F_7

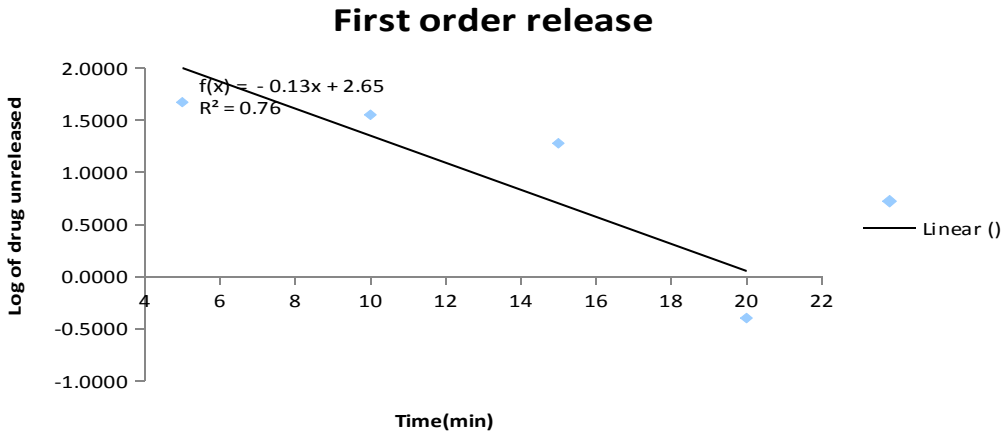

Fig45: First order release of Glipizide IR from bilayer tablets F_7

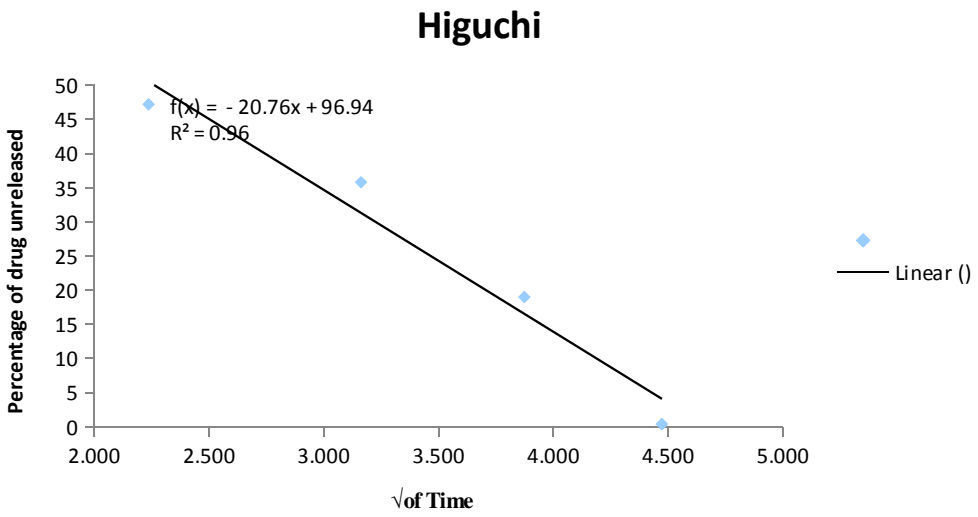

Fig46: Higuchi's kinetics of Glipizide IR from bilayer tablets F_7

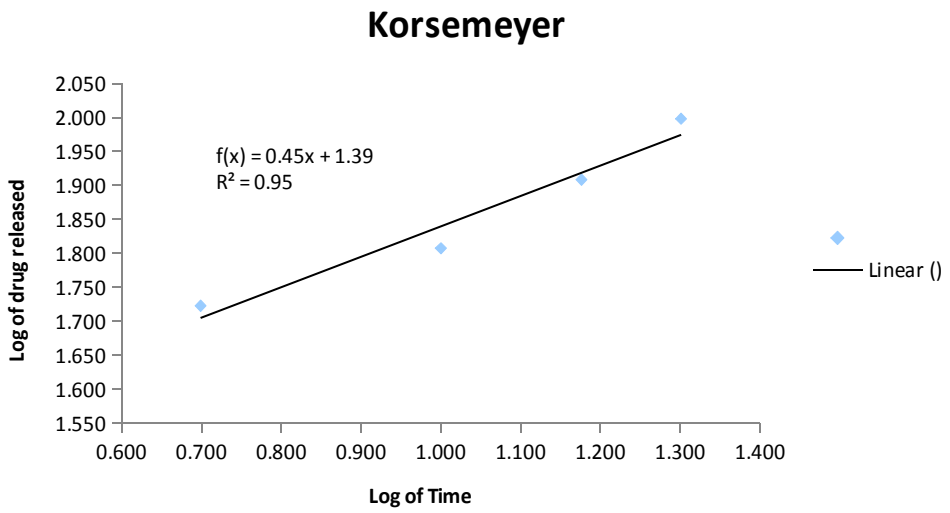

Fig47: Korsemeyer's kinetics of Glipizide IR from bilayer tablets F_7

The other evaluation tests like content uniformity test, disintegration test were performed as mentioned for the Metformin hydrochloride tablets and Glipizide tablets. The results of formulations F_1 and F_4 have been repeated for F_7.

SUMMARY AND CONCLUSION

SUMMARY

Present work relates to the development of a bilayer formulation for the effective treatment of Type 2 Diabetes.

Metformin hydrochloride and Glipizide were estimated at 233nm and 276nm respectively using UV spectrophotometry and they obeyed Beer's law in the range of 2-10µg/ml.

Compatibility studies were carried out for Metformin hydrochloride and Glipizide, and with their polymers using FTIR. No interactions were between the drugs and between the polymers.
Metformin hydrochloride SR tablets were prepared by direct compression technique using 3 different grades of HPMC polymer. The prepared SR tablets were subjected to various evaluation tests such as weight variation, drug content uniformity, friability, hardness, and in vitro dissolution study. The prepared SR tablets were found to pass all the evaluation tests. Among the 3 formulations formulation F_1 was optimized for preparation of bilayer tablet as it was found to have better release.

Glipizide IR tablets were prepared by solid dispersion technique (kneading method) using SSG as carrier. The prepared IR tablets were subjected to various evaluation tests such as weight variation, drug content uniformity, friability, hardness, and in vitro dissolution study. The prepared IR tablets were found to pass all the

evaluation tests. Among the 3 formulations formulation F_4 was optimized for preparation of bilayer tablet as it was found to have better release.

The optimized formulations were used to prepare the final bilayer tablet and all the evaluation tests done for SR and IR tablets were carried out for the final bilayer tablet. The bilayer tablets containing Metformin hydrochloride (SR) and Glipizide (IR) were found to pass all the evaluation tests that were carried out.

CONCLUSION

Metformin hydrochloride sustained release tablets and Glipizide immediate release tablets were prepared using direct compression and solid dispersion techniques respectively.

HPMC used as matrix forming polymer for the Metformin layer enables drug release for up to 9-10 hours. Among the different grades of HPMC no significant difference in the resulting Metformin release profiles from the SR layer of the tablets was found. This indicates that the viscosity of the polymer does not affect drug release rate when drug is water soluble and the dose is high. The formulation F_1 can be preferred as integrity was maintained.

Glipizide release shows that the dissolution rate of glipizide can be enhanced considerably by formulating it as a solid dispersion with SSG using kneading method. Incorporation of super

disitnegrants in the solid dispersions played a critical role in dissolution enhancement.

SR fixed dose bilayer matrix tablets containing 500mgMetformin HCl as SR from one layer and 5mg Glipizide as IR from another layer have been prepared by solid dispersion method. Formulations F1 and F_4 are selected for preparation of bilayer tablet F_7. From formulation F_7 Metformin hydrochloride and glipzide were found to be released for 10 hours and 20 minutes respectively.

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